Chem Ed

EDITORIALLY SPEAKING

Twenty-five thousand high school teachers are learning more science this summer. This number attending NSF-sponsored institutes represents about 18% of the high school science teachers in the country. We could go on at great length about the obvious importance of these statistics. We could hand out well-deserved bouquets to the many dedicated college and university scientists who have set aside other duties to make sure that institute participants get the stimulation of great teaching first hand. We could sermonize to the teachers themselves urging them to remember that Congress has considered them to be worth the investment of millions of dollars. We resist these temptations, knowing that little needs to be added to what already has been said.

Instead we are going to talk about frustrations. Our remarks are not addressed to the teachers; we are talking to readers who are citizens in communities where for years the science teacher has been the forgotten man.

What is going to happen in a few weeks when this 18% of the science teachers, stimulated by summer science institute experience, returns to the classroom? What is going to happen to the enthusiasm of the teacher who has learned dozens of demonstrations but has not one free hour in his teaching week to assemble them? What is going to happen to the ingenuity of the teacher who has devised original experiments to replace the fill-in-the-blanks exercises in the misnamed "workbook" when he is faced with forty pupils of mixed ability in a 45-minute "laboratory" period. What is going to happen to the desire for scientific accuracy in the teacher who has learned that hydronium ion is the strongest acid in aqueous solution when he is forced to use an old-edition textbook that calls hydrogen chloride an "electrovalent molecule?"

We have been set thinking about these and dozens of similar questions by a letter from Mr. Ben O. Propeck which embodies remarks he made as president of the Illinois Association of Chemistry Teachers in April, 1958. He points out that many of the conditions he mentions are being corrected, that few schools have all of these undesirables, and that the axe he is grinding is not a personal one.

> . . . We should remember that the administrators of our present system probably will be the ones who actually will supervise any changes. The average administrator is not a person chosen because of his preparation and ability in science. . . To him science may be a foreign language undesirable because of the cost of maintaining laboratories not required in other courses.
>
> . . . The problem of social promotion rears its ugly head at all levels. Not only may the teacher who fails a student be downgraded, but also there may be pressure to pass every child. . . The more proficient pupils are given busy-work while the teacher is trying to bring the slower ones up to a respectable achievement.
>
> . . . The "best" high school has the biggest gymnasium. The athlete is king, lionized by the local sports editors; his coach is a great man. Athletics represent the school in community relations. Under these circumstances it is natural that key administrative posts and policy making may be in the hands of athletic departments. The science teacher's only contact with the public may be as a ticket seller at football games.
>
> . . . Science laboratories may be nonexistent or shunted off into the inaccessible part of the school plant. The administrative conclusion that teaching five sections of a laboratory course is equal to teaching five gym classes is hardly a morale builder for the chemistry teachers.

Unhappily these and other frustrations do exist for some of the science teachers who want to use what they have learned to do a better job. Furthermore, these are grass-roots problems and broader than mere underemphasis of science.

Chemists collectively have become concerned about educational matters and many have led in community efforts to create an atmosphere of true learning in their school systems. This we applaud and urge all our readers to emulate. Mere lip service to the demands of the space age will not remove the frustrations to which we refer. More can and must be done.

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Recent Advances in Chemotherapy of Cancer

Spem successus alit or "Success lends wings to hope" is a motto which may well be attached to the search for new and effective drugs for the treatment of cancer. The scourge of cancer has afflicted mankind since the dawn of time; references to cancer have been found in the papyri of the ancients and in early Greek and Sanskrit writings. Through the ages man has attempted to find alleviation from this disease among the autochthonous drugs, namely, plant or herbal preparations. Only recently however has a determined effort been mounted in an attempt to control this disease. A campaign is underway in which a thorough search is being made to discover new types of anticancer agents and to exploit existing leads. While success comes slowly, it is evident that strong links are being forged in the chain of chemotherapeutic agents designed to bring hope to those suffering from cancer.

Cancer, or neoplastic (Gr. *neos* new, and *plasma* formation) disease, is now regarded as a family of related disorders which may be defined as a mass of new tissue which grows independently and invades surrounding structures and which has no physiological use. This definition refers to the solid tumors which, in the main, are divided into sarcomas (made up of a substance like embryonic connective tissue) and carcinomas (new growths made up of epithelial cells). The leukemias are diseases of the blood-forming organs, characterized by a marked increase in the number of leucocytes (white blood cells) and their precursors in the blood stream, together with enlargement and proliferation of the lymphoid tissue of the spleen, lymphatic glands, and bone marrow. Next to cardiovascular disorders, cancer takes the greatest toll of victims on the Western world.

However, a concerted attack on the cancer problem has taken place only within the last two decades. With the discovery of the applicability of nitrogen mustard during World War II, impetus was provided for a search for effective anticancer drugs. Four laboratories which have been engaged since the beginning of this search are the National Cancer Institute; the Chester Beatty Research Institute, London; the Children's Cancer Research Foundation, Boston; and the Sloan-Kettering Institute, New York City.

In 1954, the Congress of the United States requested the National Cancer Institute to initiate a program designed to find new and more effective agents for the treatment of cancer. As a result, there came into being, as part of the Public Health Service, the Cancer Chemotherapy National Service Center, usually abbreviated to CCNSC. A mass screening technique was decided upon and actual testing of synthetic compounds in tumor-bearing mice was begun in December, 1955. The present scope of the program may be envisaged by the fact that about 10,000 synthetic compounds and about 30,000 antibiotic filtrates are being tested each year. In addition to this routine screening, the CCNSC devotes attention to the endocrinological aspects of cancer and has developed extensive facilities for carrying out pharmacological trial of promising compounds. About 175 hospitals and medical institutions are carrying on a clinical trial program in cooperation with the CCNSC.

The screening method which is presently being used to uncover new agents may be described briefly as follows. The compound or filtrate is injected intraperitoneally into mice bearing either the Sarcoma 180 or the Carcinoma 755 solid tumors, or into mice carrying the ascites form of Leukemia L1210. These transplanted tumors characteristically show rapid growth at predictable rates. The regimen of treatment and the criteria of effectiveness are carefully established and controlled. Following the appearance of inhibition of growth against one or more of these mouse tumor systems, the compound or filtrate may be subjected to pharmacological testing in other rodents, in the dog, and in the monkey. Finally, the clinical facilities stand ready to evaluate new drugs in the human. The endocrine substances are detected by means of suitable bioassay techniques.

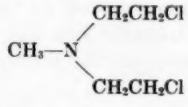
Rapid progress in the chemotherapy of human neoplastic disease has been hampered by the lack of a satisfactory test system. Tumors can be induced in animals by repeated applications of carcinogenic substances, or tumors once established can be propagated by transplanting into mice, or cancer tissue can be maintained in tissue cultures. However, results obtained in such systems cannot as yet be directly correlated with the effects of the same drug in humans. No single test system has been discovered yet which is susceptible to all compounds showing activity in human neoplasms. A finding of some activity of a compound in a transplanted mouse tumor system does not mean necessarily that it will be effective in man. For these reasons, the study of biological systems to find better testing methods continues and includes investigations of various types of tumors, both solid and ascitic (a free cellular form existing in the peritoneal cavity) forms, microbial, and tissue culture systems.

Until new agents arise from the various screening programs, reliance must be placed on those drugs which have been in common clinical use. This article is concerned with reviewing the status of the drugs which have been of value in the past and with those which are being presently developed.

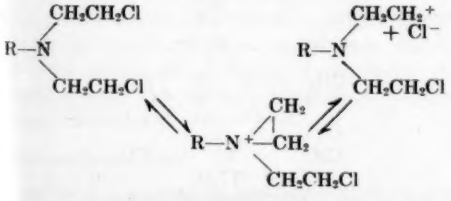
The Alkylating Agents

Cancer chemotherapy, as we know it today, gained impetus from the discovery of the anti-leukemic properties of the nitrogen mustards. On a cold winter evening during World War II, a Liberty ship loaded with 100 tons of mustard gas (bis-chloroethyl sulfide) exploded during an air raid in the harbor of Bari, Italy, throwing the vesicant mustard over the water (*1*). Other munitions vessels blew up and sank. In this blazing inferno, a thousand men gave up their lives. Those rescued from the oil-slick waters were hospitalized. Some of these developed mustard gas poisoning, characterized by a profound depression of the leucocyte (white blood cell) count, i.e., leukopenia. Since a decrease of white blood cells would be an indication of improvement in leukemia, where white blood cells are over-produced by the neoplastic bone marrow, bis-chloroethyl sulfide was tested in leukemic patients. The sulfur mustards were highly toxic and their vesicant action made it difficult to administer them by the intravenous route. However, the related nitrogen mustards, mainly bis-chloroethylamines, have been investigated as antileukemic drugs. Over six hundred nitrogen mustards have been synthesized and, while none of these compounds can be said to act as a cure for any neoplastic disease, their tumor-inhibiting effect lends hope that truly effective drugs might be uncovered.

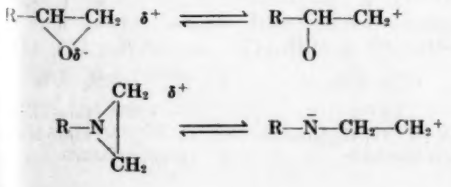
The term alkylating agent refers to alkylation of a substrate by a variety of chemical agents which, in cancer chemotherapy, may be exemplified by the nitrogen mustards. The one most commonly used clinically is methyl bis (2-chloroethyl) amine (Mustargen)



The feature common to all alkylating agents is an ability to function as an alkylating agent under mild conditions in aqueous solution, that is, under physiological conditions (*2*). With nitrogen mustards, the reactive intermediate is said to be a carbonium ion arising from a cyclic ethylenimonium ion as follows:



Other alkylating agents such as epoxides and ethylenimines may be considered as reacting by a similar mechanism, i.e., a unimolecular mechanism, in which the rate-determining step is the preliminary fission of a covalent bond.

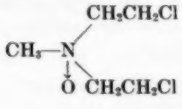


Now the carbonium ion being a positively-charged center can react with electron-rich groups in biological systems. Examples of such groups are organic and inorganic anions, amino groups, and sulfhydryl groups. It was found at the Chester Beatty Institute that agents which are especially reactive towards amino and sulfhydryl groups are not particularly good tumor-growth inhibitors. It is considered that reaction with ionized acid groups, such as the phosphate groups in nucleic acids, may be responsible for the characteristic biological effects of such alkylating agents. Reaction of primary phosphoryl groups, which occur in nucleic acids with alkylating agents, furnishes unstable triesters which, when they hydrolyze at the sugar-phosphate linkages, result in the breakdown of the nucleic acid structure. If these physical and chemical changes occurred in chromosomal material, for example, profound effects on the process of cell division would be expected.

The Nitrogen Mustards

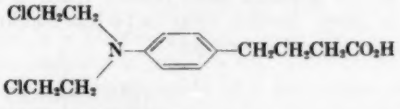
Methyl bis (2-chloroethyl) amine hydrochloride (HN_2; Mustargen) in therapeutic doses moderately depresses the peripheral blood-cell count; excessive doses cause severe bone-marrow depression with leukopenia and bleeding. It has been used in the chronic leukemias, Hodgkin's disease, lymphosarcomas, and to some extent in carcinomas of the lung and ovary. The drawbacks to the use of Mustargen have been its toxicity and its limited effectiveness against solid tumors.

The N-oxide of Mustargen, termed Nitromin, was



first prepared in the United States by Professor Mark A. Stahmann (*3*), now of the University of Wisconsin, by the action of peracids on the amine. It was developed for clinical use in Japan and has been found to have a greater margin of safety than Mustargen even though the dosage is much greater. Nitromin has been given extensive trial under CCNSC auspices in a variety of solid tumors.

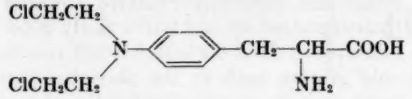
The Chester Beatty Institute has long been regarded as foremost in exploiting the nitrogen mustards as antitumor agents. It became evident that a possible means of improving the specificity of action of these drugs would be to synthesize nitrogen mustards containing amino acid or other residues which might be carried by normal transport mechanisms in the body to the site of enzymatic action. Here the amino acid residue would be hydrolyzed releasing the nitrogen mustard moiety at a specific site. This is also referred to as "latent" activity (*4*). One of the early drugs of this type was Chlorambucil or Leukeran,



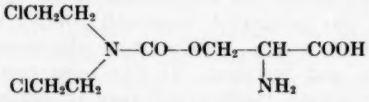
phenylbutyric acid mustard, chemically 4-{*p*-[bis-(2-chloroethyl)amino]-phenyl}butyric acid. This was synthesized at the Chester Beatty Institute and has

been used successfully in the management of chronic lymphatic leukemia and in lymphocytic lymphoma.

In preparing mustards based structurally on physiologically important compounds, the phenylalanine mustard, 3-{*p*-[bis(2-chloroethyl)amino]-phenyl}alanine,

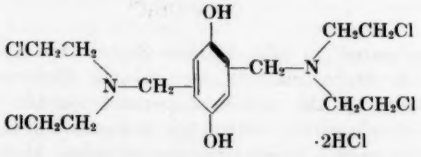


was synthesized independently in England by Bergel (*5*) and in Russia by Larionov (*6*). The racemic mixture of phenylalanine mustard is known as sarcolysin (e), the L-isomer as Melphalan. The D-isomer is said to produce as pronounced effects on the white blood cell count as the L-isomer but to have much less antitumor activity. This finding emphasizes the role that stereochemical conformations may play in future syntheses designed to produce potential anticancer agents. To emphasize this point, the scientists at the Chester Beatty Institute have discovered that the compound



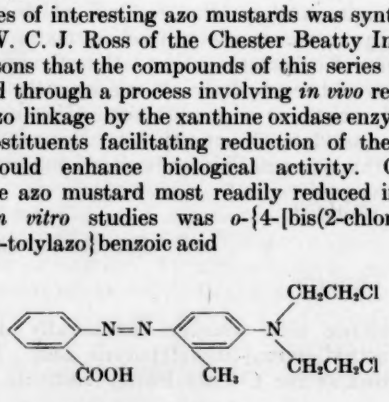
derived from serine, inhibits growth of the Walker 256 rat carcinoma, whereas the corresponding threonine derivative is inactive in this test.

One of the newer mustards recently synthesized (*7*) by Professor Carl Weatherbee, Millikin University, Decatur, Illinois, is the hydroquinone mustard, α^2, α^5, - bis(bis(2 - chloroethyl)amino) - 2,5 - xylohydroquinone dihydrochloride.



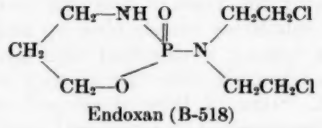
It is prepared by the Mannich base reaction of formaldehyde and diethanolamine on hydroquinone yielding the corresponding glycol intermediate. The hydroxyl groups of the glycol are replaced by chlorination with thionyl chloride or phosphorus oxychloride furnishing the mustard as the final product. This compound has produced definite inhibition of growth in animal tumors.

A series of interesting azo mustards was synthesized (*8*) by W. C. J. Ross of the Chester Beatty Institute, who reasons that the compounds of this series become activated through a process involving *in vivo* reduction of the azo linkage by the xanthine oxidase enzyme and that substituents facilitating reduction of the N=N bond would enhance biological activity. Of this series the azo mustard most readily reduced in enzymatic *in vitro* studies was *o*-{4-[bis(2-chloroethyl) amino]-*o*-tolylazo}benzoic acid



This compound, of all those in the series, produced the greatest effect against the Walker 256 rat carcinoma. It has been given limited clinical trial.

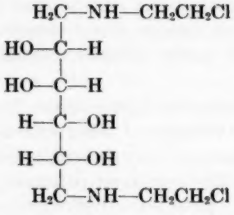
A new type of nitrogen mustard incorporating both phosphoramide and nitrogen mustard moieties in its structure has been reported very recently by the Asta-Werke firm in Germany (*9*). Its structure is:



Endoxan (B-518)

According to preliminary clinical trials, Endoxan may have some application in certain leukemic dyscrasias but is evidently of little value in treatment of carcinomas or other solid tumors. However, its activity against a variety of animal tumors is very pronounced.

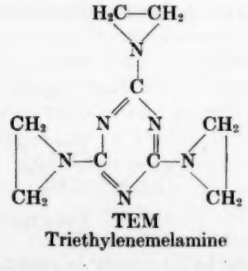
Professor L. Vargha of Hungary has synthesized a promising alkylating agent based on the sugar alcohol mannitol. It is 1,6-bis(2-chloroethylamino)-1,6-dideoxy-D-mannitol (Mannitol nitrogen mustard; BCM; Degranol) (*10*)



This alkylating agent proved to be effective in the lymphomas and leukemias but has not been studied sufficiently in the sarcomas and carcinomas.

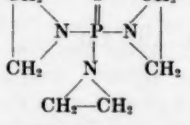
Ethylenimines

Consideration of the Nitrogen mustard postulated mechanism of action leads logically to a study of the ethylenimines (aziridines). The first one studied was 2,4,6-tris(1-aziridinyl)-*s*-triazine

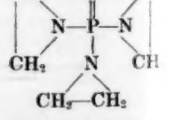


TEM
Triethylenemelamine

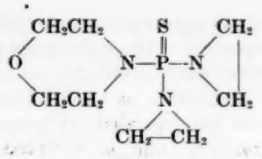
A large number of aziridines have been made, the most important of which are:



TEPA
N,N′,N″-Triethylene-phosphoramide



TSPA (thio-TEPA
N,N′,N″-Triethylenethio-phosphoramide

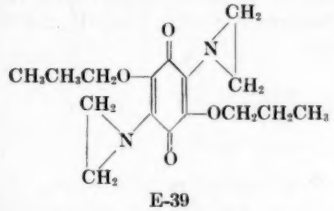


OPSPA

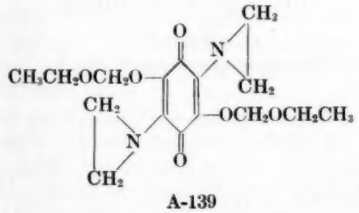
N-(3-Oxapentamethylene)-N′,N″-diethylene thiophosphoramide

TEM is effective orally but appears to be more toxic than HN_2 (nitrogen mustard) in treatment of the chronic leukemias. TSPA is preferred to the less stable TEPA and is of value in treating a variety of neoplastic conditions, including a few of the solid tumors. OPSPA (*11*) is surprisingly stable *in vivo* in contrast to TSPA and TEPA. In common with other ethylenimines OPSPA gives rise to typical bone marrow depression in most patients.

Two ethylenimine derivatives are presently undergoing extensive clinical trial. They are the ethylenimino quinones, E-39 and A-139 (*12*) discovered by the Nobel laureate Professor Gerhardt Domagk of Germany and supplied by the Farbenfabriken Bayer A. G.



E-39

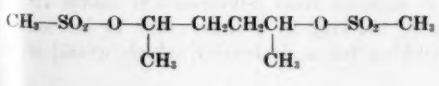


A-139

Of these two drugs, A-139 is usually preferred due to a greater solubility in physiological saline apparently due to the solubilizing influence of the oxygenated side chains. Toxicity and hematologic response in the higher animals is similar to that of nitrogen mustards. Both drugs are most effective in chronic leukemias, myeloid and lymphoid, and in Hodgkins's disease. In sarcomas, favorable though temporary results are reported occasionally.

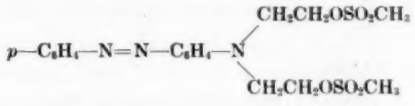
The Methanesulfonate Esters

Of a series of alkylenebis (methanesulfonate esters), $CH_3SO_3(CH_2)_nO_3SCH_3$, two possess sufficient antineoplastic activity to have found wide clinical use. These two are Myleran ($n = 4$) (*13*) and Nonane ($n = 9$) (*14*). Myleran is now an established form of therapy in chronic granulocytic leukemia, particularly since maintenance therapy can be continued without evidence of bone-marrow depression. It is ineffective against myelomas and carcinomas. The closely related compound, dimethyl Myleran (*15*)



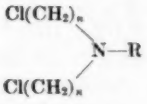
has been given trial but appears to be considerably more toxic than Myleran itself.

The sulfonoxy esters produce much less bone-marrow depression than the nitrogen mustards as well as a different hematological response. That is to say, there is a "nitrogen mustard" pattern of blood effects (fall in lymphocytes, etc.) which does not at all resemble the Myleran pattern. It was of interest, therefore, to study the activity of a compound such as



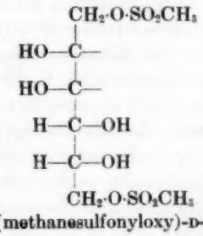
at the same time as the corresponding "azo" mustard (CB2222). The Chester Beatty Institute group (*16*) found that the compound shown above, although a mesyl ester type, produced the "nitrogen mustard" pattern of blood effects.

The mesyl esters also afforded an opportunity to study stereochemical influences on biological activity of these compounds. Unsaturation in the Myleran type of molecule, as in $CH_3SO_2{\cdot}O{\cdot}CH_2{-}C{\equiv}C{-}CH_2{\cdot}O{\cdot}SO_2CH_3$ (*17*), fixes the positions in space of the active mesyl groups. The Chester Beatty group found this compound to be inactive against the Walker rat carcinoma 256. Also, since increasing the chain length in nitrogen mustards, i.e.,



where $n>2$, results in greatly diminished antitumor activity, it is evident that the architecture of the molecule plays an important role in at least some of the alkylating agents.

It should be noted here that recent animal experiments with "mannitol Myleran (*18*) indicate that this relative of Degranol may be worthy of attention.



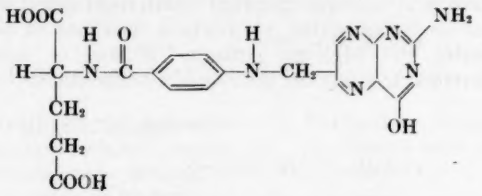
1,6-Bis(methanesulfonyloxy)-D-mannitol

The compound is of low toxicity and appears to be without effect on the blood elements, and is being given clinical trial in England and in the United States.

Antimetabolites

An antimetabolite is a compound whose biological activity depends on interference with synthesis or utilization of a normal metabolite in the body. For example, compounds are known which function as antagonists of amino acids and of vitamins. The most important classes of value in cancer chemotherapy are the antifolic acid compounds, and analogues of purines and pyrimidines. Folic acid deficient animals develop anemia and severe cytopenia. Studies in

bacterial nutrition indicated an interchangeability between folic acid and thymine, thus suggesting a role for folic acid in the formation of nucleic acid and further emphasizing the role of this dietary factor in cellular proliferation. Its structure is:

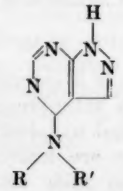


Folic acid (Pteroylglutamic acid—PGA)

Sidney Farber, Children's Cancer Research Foundation, Boston, discovered that an analogue of folic acid, 4-aminopteroylglutamic acid (Aminopterin; the hydroxyl at the 4 position in the pteridine ring of PGA has been replaced by an amino group) was an effective agent for the treatment of leukemia in children (*19*). This important finding gave a tremendous impetus to the chemotherapy of cancer and to study of folic acid analogues. Of these analogues or antimetabolites, Amethopterin (4 - amino - N^{10} - methylpteroylglutamic acid) is the most successful; in combination with 6-mercaptopurine and cortisone, it will in some children, eradicate all signs, symptoms, and laboratory evidence of acute leukemia. The child, to all appearances, is returned to health and happiness. Unfortunately, the disease returns and further treatment with the anti-folic drugs is futile owing to the development of resistance to the drugs. Amethopterin treatment of the folic acid dependent tumor, chorioadenocarcinoma, is causing dramatic remissions in this cancer which annually claimed the lives of several hundred pregnant women in the United States alone (*20*).

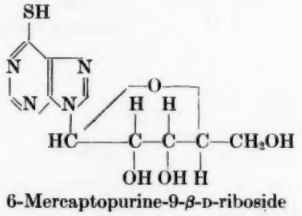
This phenomenon of resistance is most baffling and is being accorded the widespread investigation it deserves. An associated phenomenon is the related cross resistance exhibited by the host towards members of a given series. For example, administration of 6-chloropurine to leukemic patients arrests (for a short while) the course of the disease. However, when the disease recurs, treatment with 6-chloropurine is, by and large, ineffective and so, too, is treatment with 6-mercaptopurine, even though the latter compound is effective by itself initially against the same type of cancer. Therefore chemists have searched for purine antimetabolites which would overcome the difficulty of cross resistance.

R. K. Robins, Arizona State University, developed the 4-aminopyrazolo (3,4-*d*)pyrimidines (*21*)

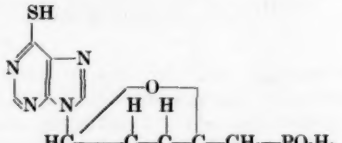


which are structural variants of the purine adenine and which are effective against the cross-resistant tumors. Unfortunately, the aminopyrazolo pyrimidines produce liver damage, which, while reversible, has slowed acceptance of these drugs as clinical agents. Robins has further shown that the related 4,3-*d* series are completely ineffective as tumor-damaging agents. While this must be regarded at present as an interesting observation, one is tempted to speculate that the chemist must look into the chemical reactivity of anticancer compounds. For example, we do not have sufficient information on the relative tendencies of heterocyclic ring systems to undergo ring cleavage. This subject is presently being dealt with in detail by the interesting work of Edward C. Taylor, Princeton University, among others.

Antimetabolites may be arrived at by designing slightly altered variant structures of compounds essential to cell metabolism. From the foregoing it is clear that this may be done, for example, by replacing the hydroxyl by a halogen or amino group, or by interchanging adjacent carbon and nitrogen atoms. The molecules so changed should, however, be in the form found in physiological states or acceptable to biochemical reactions. For example, the purines are known to occur as the ribosides and ribotides in nucleic acids, so that it would be logical to investigate the activity of 6-mercaptopurine riboside and 6-mercaptopurine ribotide.



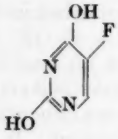
6-Mercaptopurine-9-β-D-riboside



6-Mercaptopurine-9-β-D-ribotide

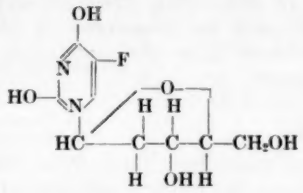
The riboside was found to have a better therapeutic index in experimental animals and is presently in clinical trial. Preliminary reports are encouraging.

Another variant, but in the pyrimidine series, is 5-fluorouracil developed by Charles Heidelberger (22), McArdle Memorial Institute, University of Wisconsin, in collaboration with the Hoffman-LaRoche Company.



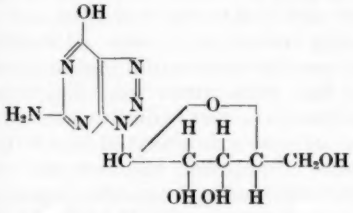
This compound showed some effect on solid tumors, particularly those of the gastrointestinal tract. However, it appears that 5-fluorouracil exerts its tumor-damaging activity at a dose close to its toxic level. In searching for a derivative which would show less

toxicity but retain tumor-damaging properties, the deoxyriboside of 5-fluorouracil,



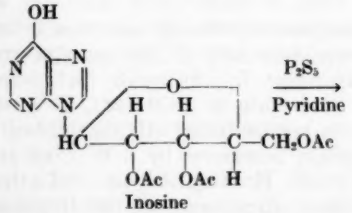
5-fluoro-2′-deoxyuridine, was prepared by an enzymatic reaction involving thymidine and 5-fluorouracil. The resultant deoxyriboside has, in preliminary trial, appeared to possess a more favorable therapeutic ratio than the parent purine base and is being tried clinically.

With respect to the ring variants where a carbon atom of the purine ring is replaced by a nitrogen atom, R. Y. Moir, Queen's University, Canada, is preparing 8-azaguanine riboside

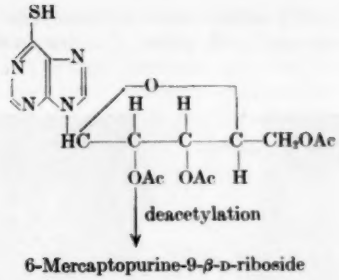


for trial by the Cancer Chemotherapy National Service Center. Undoubtedly we will see more activity in this general field as we learn more about cellular metabolism. In this connection, future work will undoubtedly include appropriately substituted nucleosides and nucleotides.

A definite advance in this direction has been made by the Sloan-Kettering Institute, which has been proceeding with the synthesis of ribosides available through a thiation reaction (*23*) studied by J. J. Fox of that Institute. For example, inosine is treated with phosphorus pentasulfide in pyridine solution to yield 6-mercaptopurine riboside according to the following scheme:

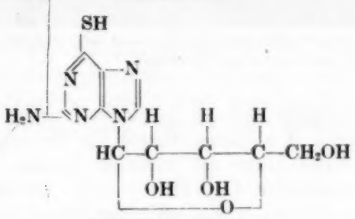


Inosine



6-Mercaptopurine-9-β-D-riboside

In an extension of this reaction, Fox synthesized thioguanosine from guanosine. Preliminary clinical trial is underway with thioguanosine.



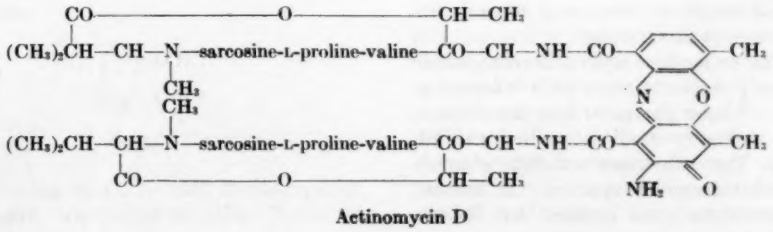
Thioguanosine

The next logical step would be to make the corresponding ribotide, thioguanylic acid, and other members of the purine series. It is interesting to note however, that the biological activity of effective purines is not improved by their conversion to the ribosides. For example, 6-chloropurine riboside possesses a very greatly lowered activity compared to the free base.

Natural Products

Antibiotics or Substances of Microbial Origin

The advent of penicillin and streptomycin ushered in a new era in medicine. It would be logical, following the demonstration of the extreme specificity exhibited by the antibiotics, to search for effective anticancer agents in products from microbial systems. In fact, one antibiotic, Actinomycin D, has already been found by Farber (*24*) to be a uniformly successful treatment for Wilm's tumor. This tumor is one which occurs in children and which is associated with kidney destruction. Actinomycin D, however, is an extremely toxic substance (LD_{50} in mice = 1.7 mg/kg) and must be administered by one skilled in its use. Chemically, the actinomycins differ in the composition of their polypeptide side chain but apparently possess the same chromophoric group. The order of the amino acids in each of the side chains of Actinomycin D has been established as (*25*) L-threonine-D-valine-L-proline-sarcosine-L-N-methyl-valine. The structure of Actinomycin D is therefore:



Actinomycin D

Actinomycin C_3 differs from Actinomycin D only in having *alloiso*leucine in place of valine in the peptide chain (*26*).

Remarkable effect produced by treatment with Actinomycin D (*right*) compared with untreated mouse tumor (*left*).

The photograph shows the dramatic effect obtained on treatment of a mouse tumor (in this case, a solid tumor derived from an initially ascitic neoplasm) with Actinomycin D. The control or non-treated mouse on the left has a well developed tumor mass while that on the right shows, after treatment of an identical tumor with Actinomycin D, no sign of the disease. This remarkable feat can be demonstrated repeatedly and uniformly in mice. However, translation to the human has been as uniformly unsuccessful except for treatment of the Wilm's tumor.

To exploit the inherent possibilities of finding effective anticancer substances among the antibiotics, the Cancer Chemotherapy National Service Center is testing some 30,000 antibiotic culture filtrates per year. These are obtained in the following way. A microorganism is isolated by the usual bacteriological techniques from a soil sample which may originate in almost any spot in the world. The isolated organism is then cultured in a broth medium and then filtered. The filtrate is immediately frozen in Dry Ice and shipped to one of the Cancer Chemotherapy National Service Center screening contractors. Most of these filtrates are submitted by pharmaceutical companies in the United States, who are responsible for fractionation and isolation of the active components in the instances where activity is shown by one of the filtrates.

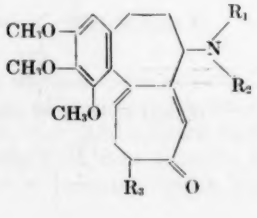
Newer developments in this field can be illustrated by reference to the antibiotic Mitomycin. It is a recently discovered antibiotic which is active against bacteria as well as a very wide spectrum of mouse tumor systems. It was isolated by Dr. Tojo Hata and his associates at the Kitasato Institute for Infectious Diseases, Tokyo, from a soil sample taken in that vicinity. The organism proved to be a new species of *Streptomyces* given the name, *Streptomyces caespitosus sp. nov.* Hata, *et al.* (*27*), have isolated three fractions, A, B, and C, from mitomycin. Their structures are unknown as yet, although an empirical formula of $C_{26}H_{33}NO_{12}$ has appeared in the literature.

Mitomycin C is a lavender-blue crystalline compound and is a comparatively stable fraction with interesting anti-tumor activity. Under the polarizing microscope it appears as clusters of very small rods which exhibit parallel extinction. The substance exhibits characteristic infrared and ultraviolet spectra. A limited quantity of this antibiotic was isolated by Bristol Laboratories, Syracuse, N. Y., under a contract with CCNSC. Clinical trials are in progress using this supply of Mitomycin. Beyond doubt, startling developments will be uncovered in the antibiotic area in the course of present and future searches for anticancer agents.

Plant Products

In the past, plants have furnished an imposing array of medicinals for the medical armamentarium, such as digitalis, quinine, belladonna, strychnine, ephedrine, the Rauwolfias, antibiotics, etc. It would be deemed logical to search for anticancer agents among the multitudinous components of terrestrial and marine flora. Primitive man had recourse only to autochthonous medicinals, that is to say, the herbs and simples of centuries past. A search for information on these early drugs is being made by Dr. J. L. Hartwell of the Cancer Chemotherapy National Service Center. He has been surveying the world's literature from ancient to modern times for references to plants which had been used in some form or other in the treatment of neoplastic and related diseases. A surprising number of plants used for treatment of cancer, warts, and other growths has been uncovered. To investigate the potentialities of the world's flora implicated as a possible source of anticancer drugs would be a formidable task. While no concerted effort has been made to test these plants systematically, a modest attempt has been made in this direction by the CCNSC. Some 600 extracts from plants collected in the United States, South America, and South Africa by the Eastern Utilization Research and Development Division of the United States Department of Agriculture, in the search for sapogenins which would serve as precursors of cortisone, have been submitted for screening in the CCNSC program. In addition, several hundred more have been sent to CCNSC by the University of Arizona and by other institutions and individual chemists. A plant products program to include specimens of the widest possible variety of genera of higher plant orders is under active consideration.

There have been a few substances of plant origin which have been afforded trial in cancer. The best known of these is undoubtedly colchicine which is a yellow, water-soluble alkaloid occurring in members of the Liliaceae, especially in the autumn crocus, *Colchicum autumnale L.* Although first isolated in a relatively pure state in 1820 (*28*), its structure has only recently been satisfactorily established through a series of brilliant researches by J. W. Cook at Glasgow, and by Tarbell, Horning, Ullyot, and others in the United States. Acceptance of the tropolone methyl ether structure first advanced by Dewar (*29*) for ring C of colchicine leads to the following structure for colchicine and its derivatives.



Name	R_1	R_2	R_3	LD_{50} (mg/kg) (mouse, i.p.)
Colchicine	H	$COCH_3$	OCH_3	1.0
N-Methyldeacetylcolchicine (Demecolchin)	H	CH_3	OCH_3	8.0
N-Methylcolchicine	CH_3	$COCH_3$	OCH_3	4.3
N-Methylcolchicine	CH_3	H	OH	500
N-Deacetylthiocolchicine	H	H	SCH_3	..
Trimethylcolchicinic acid	H	H	H	..

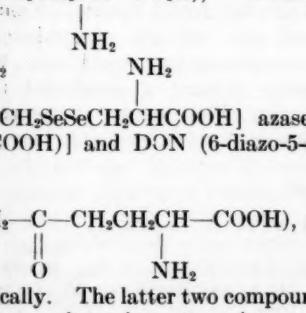
Colchicine has been used for many years as a specific agent for the treatment of gout and its now recognized ability to arrest mitosis (at the early metaphase) of plant and animal cells has found important applications in horticulture and cancer research. Trial of colchicine in experimental animals bearing a wide variety of tumors, including spontaneous mammary carcinomas, demonstrated modification of tumor development but, in general, no appreciable prolongation of survival time. In order to effect tumor regression, doses of colchicine far in excess of those required to arrest mitosis must be employed, and this occurs near the minimum lethal dose. When regression does occur, it is primarily the result of vascular damage. Treatment of human neoplasias with the alkaloid presents the same difficulties. Derivatives of colchicine (e.g., those listed in the above table) have been given laboratory and, in some cases, clinical trial. Deacetylcolchicine, demecolchin, and N-deacetylthiocolchicine are most effective against chronic myeloid leukemia; however, demecolchin is apparently not as reliable as Myleran (*30*).

A number of other alkaloids exhibit antimitotic properties, notably emetine and narcotine.

Another antimitotic agent, podophyllotoxin, a lignan found in podophyllin resin, has been tried clinically with discouraging results (*31*).

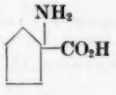
Amino Acid Antagonists

Most amino acid antagonists, such as ethionine ($CH_3CH_2SCH_2CH_2CH(NH_2)CO_2H$), selenium cystine



[HOOCCHCH$_2$SeSeCH$_2$CHCOOH] azaserine, [(N$_2$CCH$_2$CH—COOH)] and DON (6-diazo-5-oxo-L-norleucine, N$_2$CH$_2$—C(=O)—CH$_2$CH$_2$CH(NH$_2$)—COOH), are too toxic for use clinically. The latter two compounds, azaserine and DON, act as glutamine antagonists.

In the CCNSC program attention was focused early on the amino acids. A sample of 1-aminocyclopentanecarboxylic acid



was submitted for testing by C. I. Noll, Pennsylvania State University, and was assigned the National Service Center code number NSC-1026. Dr. Noll had resynthesized this compound following methods described in German journals *ca* 1890 to study its physical properties. Primary antitumor screening indicated that it inhibited growth of Carcinoma 755 and of Sarcoma 180 mouse tumor systems. On studying the effect of this compound on weight loss and mortality of mice, and dose-response tests, it was evident that it was more specific towards the Carcinoma but also that its lethal effects were delayed. However, on pharmacological examination of the substance in the dog and the monkey, it was found that greatly increased doses were tolerated in the dog and that massive doses were required in the monkey before toxic symptoms began to appear. It is questionable if this compound will be an effective clinical drug. The assumption could be made that NSC-1026 would function as an amino acid antagonist since it can be looked upon as an amino acid lacking the usual α-hydrogen atom. This hypothesis remains to be clarified.

Adjuvant Therapy

A review of cancer chemotherapy would be incomplete without reference to the use of drugs as an adjuvant to surgical procedures. When a localized tumor is excised, the surgeon's manipulations dislodge many cancer cells, which can be carried to other parts of the body via the blood stream and new tumors begin to grow at new sites. This process is similar to spontaneous metastasis. Preventive measure include lavage of the surgical wound and administration of chemotherapeutic agents to kill those cancer cells remaining at the site of surgery or those circulating in the blood stream. This use of anticancer agents is commonly referred to as adjuvant therapy.

Nitrogen mustard and thio-TEPA have been the chief antitumor agents employed in adjuvant therapy of cancers of the stomach, lung, and other organs. Even though these compounds are known to inhibit blood-clotting and wound healing, their use as adjuvants in surgery may become more general.

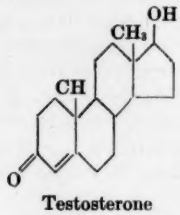
The Hormones

Tumors of the reproductive organs are known to be hormone dependent. Other neoplastic tissue retains to a greater or lesser degree some dependency on endogenous hormones for maintenance of growth. Cancer of the breast and prostate often depend on the same hormones which governed the life and functions of the parent organs.

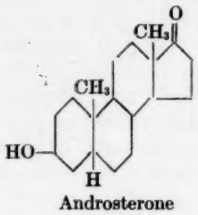
In 1951 it was discovered that tumors of the sex organs could be controlled at times by bilateral adrenalectomy. In other words, removal of the hormone-secreting gland removes the source and flow of the hormone responsible for growth of the sex organ.

It was then logical to alter the hormonal balance by utilizing the female sex hormones to treat cancer of the prostate and the male sex hormones to alleviate cancer of the breast. Thus, estrogens are administered for cancer of the male sex organs and androgens for cancer of the female sex organs. Since the pituitary hormones common to both male and female govern production of sex-specific hormones, therapy of hormone-sensitive tumors by the appropriate androgen or estrogen is alluded to as "chemical hypophysectomy."

Testosterone, usually employed as the acetate or propionate ester, is the standard androgen used in certain types of advanced breast cancer. Its use is limited by the occurrence of masculinizing effects. Certain androsterone derivatives have also been employed.

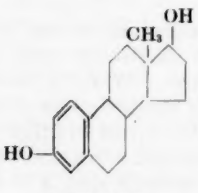


Testosterone

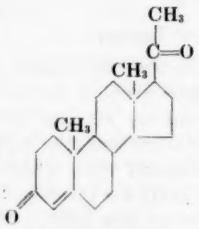


Androsterone

The estrogens employed in prostatic cancer have included estradiol esters and the stilbestrols. Progesterone, the progestational hormone, is employed as an "antiandrogen."

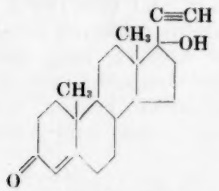


Estradiol



Progesterone

The 17 α-ethynyl derivative of testosterone has only about one-third the activity of progesterone by subcutaneous injection; however, it is much more active than progesterone on oral administration.



17 α-Ethynylprogesterone

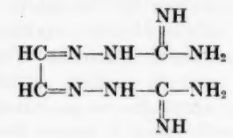
Of the adrenocortical hormones, cortisone and cortisol are used in the management of acute leukemia in children. Routinely, cortisone, 6-mercaptopurine, and Amethopterin are the drugs of choice in this disease. The more specific hormone, prednisolone, has been used in the treatment of multiple myeloma.

Halogenated corticoids could be referred to as antisteriods and are being accorded attention for this reason. The most active appear to be the 9-fluoro steroids, e.g., 9 α-fluoro-11-hydroxy-17 α-methyl-testosterone and 9 α-fluorocortisone.

As part of a search for antiandrogens and antiestrogens, it would be logical to examine the so-called azasteroids and other steroids in which a carbon atom has been replaced by nitrogen, sulfur, or other heterocyclic atom. These are difficult syntheses but more chemical activity is expected in this area. In addition, it would be expected that transformation products of the triterpenes might possess unusual physiological activities.

New Types of Agents

In a review of this kind, an example of new types of drugs being uncovered in this massive attack against neoplastic disease should be given. B. L. Freedlander and Frederic A. French of the Mount Zion Hospital, San Francisco, have been synthesizing organic compounds as potential chemotherapeutic agents for some years past. Recently they found (*32*) that certain bis (guanylhydrazones) possessed a high degree of effectiveness against mouse leukemias. In particular, glyoxal bis (guanylhydrazone)



and the corresponding methyl glyoxal bis (guanylhydrazone), as the sulfate or other appropriate salts, markedly prolonged the life span of leukemic mice. It is the more remarkable since these compounds are effective only by oral administration. The CCNSC is cooperating in this study by making large amounts of these substances available for pharmacological and clinical trials. Undoubtedly, more will be heard of this class of antitumor agents. This is only one example of newer drugs which are being discovered and which are steadily being brought to light. Others will follow.

The path leading to these new discoveries has been long and arduous, fraught with many frustrations and failures and studded with the sterling efforts of many and diversely-trained scientists. These efforts are being aided and brought to fruition by the generosity of the people of the United States who, through the Congress of their country, are providing funds for a determined attack on cancer. We at the CCNSC are confident that this generosity of thought and provision will yield new and more effective agents for the treatment of this dread disease. From the foregoing exposition, the onslaught of combined forces in laboratories throughout the world may be seen as forging pathways toward a successful solution of neoplastic disease. Well might it be said at the present time that success lends wings to hope.

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Safety Practices: Industry, Yes—Colleges, ??

Literature concerned with safety is constantly placed before the chemist. *Chemical and Engineering News* devotes a section to safety features and new safety information. Typical topics recently covered are modern safety aspects of: radiation protection (*1*, *2*); amateur rocketeering (*3*); boron compounds (*4*); and disaster aid (*5*). Information of general interest as well as advice and suggestions of specific value are reported. Whether or not the advice is accepted and heeded is a question which is quite difficult to answer. A safety guide, prepared by a committee of industrial chemists, has also been published (*6*). Suitable safety posters are available for bulletin-board use at nominal cost (*7*). Other safety literature is available at no charge (*8*).

When academic staff members visit industrial laboratory installations, they are usually impressed by the safety practices in operation. *No Smoking* signs, safety record charts, presence of fire extinguishers, and location and number of safety showers, as well as emergency fire alarm stations are all easily identified and quite numerous. Since these items are quite expensive to install and maintain, it is only logical to consider that industry considers the cost of such items thoroughly justified. Industry has "safety engineers" who are most cooperative in sharing ideas and suggestions relative to safety practices with anyone expressing a desire for such information (*9*).

As a general rule industrial laboratories are more safety-conscious than most academic institutions. Safety slogans, posters, suggestion boxes, and committees are very common in industry, but somewhat unusual in academic laboratories. Some large university laboratories observe modern safety practices in the storage, issuing, and use of hazardous materials. On the other hand the smaller academic institutions (often with the chemistry laboratory on the upper floor of an old building) have many practices which are dangerous. Moreover, they are doing little or nothing to remedy the situation. Experience with one or more avoidable accidents does much to cause an institution to become safety conscious (*10*).

Good Practices

Examples of safety practices which are often neglected at the small institutions are:

A university chemistry stockroom unpacks all glassware shipped in cardboard containers (plus excelsior) and stores it in *steel trays* in *steel shelving*.

A modern laboratory has been designed so that all offices and laboratories have two entrance (or exit) doors.

New university laboratories have an underground storage vault for volatile flammable solvents so designed that in the event of excessive heat (fire) an automatic regulated carbon dioxide atmosphere floods the area.

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A state university has a bulk chemical storage area in which phosphorous containers are placed on the floor in a "well" so designed that, in the event of fire, the operation of an automatic sprinkler system would result in flooding the "well."

A state university has a coin (for pay telephone use) located in each departmental emergency cabinet. Access to the cabinet is gained by breaking a microscope-slide seal covering the catch on the lock. No key is involved.

Bad Practices

How many of our well meaning academic friends have not smoked a cigar or cigarette in a laboratory containing strong ether or benzene fumes? This is not done in industrial laboratories. Why do the professors (who should—and do—know better) violate common sense?

Another source of safety hazard in many academic institutions is the accumulation of a supply of surplus hazardous chemicals (usually at no cost) from well-meaning industrial or governmental sources. Speaking from first hand information, we have located several one-half ounce bottles of hydrocyanic acid in a dark corner of our stockroom and 32 one-ounce bottles of picric acid in another. This had been received some years before. We had no real use for the hydrocyanic acid, and the annual use of picric acid approximates four ounces. Recently one of our industrial friends was planning to dispose of 33 pounds of perchloric acid, but realized that "an area college could possibly use it." They obligingly gave it to us. About ten days after its arrival, a staff member found it neatly packed in excelsior in our stockroom. Luckily none had spilled and no one happened to drop any hot cigarette ashes on any of the excelsior. These "gifts" from industrial or governmental laboratories are welcomed, but it is most essential that someone with adequate technical knowledge and safety consciousness be at hand to classify and store them on arrival. It is entirely possible that such items could be received and stored indefinitely in this hazardous packing, had it not been "accidentally" discovered by one who understood the danger.

Based upon these typical experiences it is well to recommend that colleges should accept only such quantities of hazardous chemicals as they can utilize in a reasonable period of time. In this day of limited budgets and need of expensive equipment, many see a material saving if excessive quantities of hazardous materials are accepted and "held for future use."

Constant Evaluation Necessary

Although check lists of safety practices and principles have been published (*11*, *12*), it is well to reconsider certain rules which can be applied in all chemical laboratories with a minimum of expense. If those in charge of academic laboratories would use the following minimum list of items in a self-evaluation of safety conditions and practices. most would be surprised, if not ashamed. We are sometimes prone to *talk* about rules, yet we hesitate to *do* something about them.

(1) Are safety practices and principles continually brought before the staff and student body?
(2) Do the staff members abide by standards of safety established for students?
(3) Are emergency cabinets restocked and checked at specific intervals?
(4) Are storage areas free from excessive packing and flammable materials?
(5) Are persons in charge of receiving and stocking equipment and chemicals familiar with the toxic and flammable nature of all materials they handle?
(6) Are cylinders of compressed gases "chained" in an upright position using a home-made device or a commercially available clamp (*13*)?
(7) Are electrical gadgets connected to a "spider-web" of extension cords with two and three-way outlets—all originating at a single wall outlet?
(8) Is a public telephone available for emergency calls during regular as well as off-hour periods? Are coins available for general use by pay-phone stations at such times?
(9) Is a "Safety Committee" composed of students and faculty active? Are its recommendations recognized?
(10) Are staff members advised regarding basic first-aid practices for each of several possible types of laboratory accidents?
(11) Are safety showers tested at a definite time interval?
(12) Are fire extinguishers checked on a definite time schedule?

If a new laboratory or extensive alterations of existing facilities are being planned, it is obvious that many safety factors, possibly entailing some modifications in plans, should be incorporated in the program.

It is firmly believed that area industrial safety engineers would be very happy to evaluate the safety status of local colleges. Their suggestions and comments should be considered by the faculty and administration of the schools involved. The responsibility for invitation of such "inspections" rests with the academic faculty concerned. Thus more understanding and recognition of evident problems and shortcomings will be clearly defined and remedial measures provided.

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Notes on Qualitative Analysis

EDITOR'S NOTE: The following papers have been collected over a period of months. A similar collection appeared a year ago (J. CHEM. EDUC., **35**, 401 (1958)). It is the Editor's hope that collection into one place will prove more attractive to readers than the more frequently used editorial procedure of scattering items such as these through the pages of several issues. We apologize to authors who thus have had to wait to see their work in print.

We commend to readers' attention the fact that several of these represent the solution of problems given to freshman students in qualitative analysis courses. We hope that publication in these pages can stimulate just such activity. If readers merely incorporate these ideas into their own laboratory instructions, our battle is only half won. If, beyond that, these ideas suggest to the readers that they use their own ingenuity in similar fashion, we are gratified.

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A Spot Test Analysis of the Group III Cations

This procedure may be used for the direct determination of the Group III cations, for a quick confirmation of the results obtained in the regular scheme of analysis, or for teaching another technique in analytical chemistry. With little practice the average student can do an unknown in about an hour. In the method offered here, the available spot tests have been selected and arranged such that each Group III cation may be detected in the presence of all the others provided these cations are present in approximately the same molarity.

An alternate method utilizing most of these tests as paper spot tests is provided. The prepared papers are usually more stable and are easier to store and to dispense to the student than are the reagents.

About 250 students have tried these tests over the past few years on unknowns containing about 1 mg of cation per ml. On the average these students did almost as well on this more rapid method as they did in the more time-consuming traditional method. Since this procedure is designed for a beginning course, interfering anions such as borates and phosphates are not present, nor is organic matter usually in the unknown.

Students are instructed to try these tests on solutions containing the individual cations until they are familiar with the appearance of positive results. Then they practice on a known solution containing all these Group III cations. The tests are conveniently performed on a spot plate using small drops; quantities are increased only if the results are vague and indefinite. There is no preferred order in which these cations may be determined.

Nickel

Reagent: 1% dimethylglyoxime in ethanol.

To a drop of the test solution is added one drop of conc. NH_3 and 2 or 3 drops of dimethylglyoxime reagent. The formation of a pink or red color on the spot plate indicates nickel. If the results appear to be negative, add another drop or two of NH_3 before discarding.

Paper spot test: Filter paper is soaked in 1% dimethylglyoxime in ethanol and dried. A drop of conc. NH_3 is added to the dimethylglyoxime paper. To this is added a drop of the solution under test, followed by the addition of several more drops of NH_3. If nickel is present a bright pink stain will appear on the outer edge, usually within a minute.

Note: It is best to perform these paper spot tests in groups of three, one on the cation alone, one on a solution containing all the Group III cations, and a third on the unknown. Direct comparisons may then be made before any of the spots have had a chance to change color through drying.

Iron(III)

Reagent: 1% KCNS solution.

A drop of the test solution is added to a drop or two of the KCNS reagent on a spot plate. A red color appears.

Paper spot test: Filter paper is soaked in 1% KCNS and dried. A drop of the test solution is added to the prepared paper. A deep red or brown stain indicates iron.

Cobalt(II)

Reagent: 1% alpha nitroso beta naphthol in acetone.[1]

A drop of the test solution is mixed on a spot plate with a drop of the reagent. A few drops of 10% Na_3PO_4 solution are added. A brown coloration indicates cobalt.

Paper spot test: A drop of 6 *M* HCl, a drop of the test solution, and an additional drop of HCl are added successively on top of each other on ordinary filter paper. The paper is then heated over a low flame until it is on the verge of scorching. If cobalt is present a blue or green color will appear.

Aluminum

Reagents: Filter paper soaked in 5% $K_4Fe(CN)_6$ and dried. Saturated alizarin in ethanol.[2]

A small drop of the neutral or weakly acid test solution is placed on the $K_4Fe(CN)_6$ paper. Other Group III cations that may be present are precipitated as the insoluble ferrocyanides. Any aluminum ion present diffuses beyond this precipitate. A drop of alizarin is added to the zone outside the precipitate. The paper is held over ammonia and dried. A red color appears which is not conclusive at this point. The paper is washed in

[1] FEIGL, FRITZ, "Spot Tests, Inorganic Applications," 4th ed., Elsevier Publishing Co., New York, **1954**, Vol. 1, p. 138.
[2] *Ibid.*, p. 179.

boiling water for at least two minutes. A red ring, the alizarin aluminum lake, indicates the presence of aluminum.

Manganese(II)

Reagent: $NaBiO_3$ solid.

Chloride ion is removed by adding $AgNO_3$ solution. The solution is centrifuged and the precipitate is discarded. The solution is diluted with an equal volume of water and a drop of this is then placed on the spot plate. A pinch of $NaBiO_3$ is added. A purple color which may soon turn brown confirms manganese.

Chromium(III)

Reagent: 1% diphenylcarbazide in ethanol.[3]

A drop of the test solution is made alkaline with a drop or two of 6 *M* NaOH. Sodium or hydrogen peroxide is added cautiously, then warmed, until chromate is formed. The solution is acidified. *Important:* Check for acidity with litmus. A drop of the diphenylcarbazide reagent is added. A violet color indicates chromium.

Zinc

Reagent: Dithizone in CCl_4 (10 mg of diphenylthiocarbazone in 100 ml CCl_4).[4]

A drop of the test solution is mixed on a watch glass with a drop of NaOH and a few drops of the dithizone solution. The CCl_4 is evaporated by blowing. A raspberry red solution which may appear first along the outer edge shows the presence of zinc.

Paper spot test: Filter paper is soaked in the dithizone solution listed above, and dried. One drop of the test solution and 4 drops of 2 *M* NaOH are mixed on a watch glass. The diphenylthiocarbazone paper is pressed into the mixture. If zinc is present, a pink stain will appear.

[3] *Ibid.*, p. 161. Procedure modified by the authors.

[4] *Ibid.*, p. 172.

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Qualitative Test for Potassium Using Sodium Tetraphenylboron

Sodium tetraphenylboron, $Na(C_6H_5)_4B$, reacts with potassium ions to form a white insoluble compound. The equation for the reaction may be written as follows:

$$(C_6H_5)_4B^- + K^+ \rightarrow K(C_6H_5)_4B$$

Sodium tetraphenylboron was first prepared by Wittig and co-workers (*1*, *2*, *3*) in 1949, and since that time a number of methods have been developed for use of this reagent in the quantitative determination of potassium. A comprehensive bibliography from 1949–58 is given by Barnard (*4*) and Barnard and Büechl (*5*).

A number of qualitative procedures are available using $Na(C_6H_5)_4B$ for the detection of K^+ by itself or in the presence of certain specific cations (*6*, *7*, *8*, *9*, *10*). The only methods using $Na(C_6H_5)_4B$ for the detection of K^+ in general cation unknowns (*11*, *12*, *13*) suggest testing for K^+ in the "soluble cation" group. These procedures further specify either the prior removal of NH_4^+, which also forms an insoluble compound with the reagent, or the distinction of K^+ from NH_4^+ by flame testing the precipitate. In this communication a method is described which uses $Na(C_6H_5)_4B$ to test for K^+ in original general cation unknown solutions. This test resulted from the observation that $K(C_6H_5)_4B$ is insoluble in NaOH while $NH_4(C_6H_5)_4B$ is soluble. The method, which eliminates all interfering ions by a one step treatment with NaOH, is specific for K^+, and hence the need for flame testing the precipitate is eliminated.

The concentration of the reagent was found to be a critical factor in the practical success of the test, an unnecessarily high concentration resulting in sensitivity to traces of K^+ in many common reagents. Most of the qualitative and quantitative procedures for the analysis of K^+ using $Na(C_6H_5)_4B$ recommend the use of a 1–4% solution of the reagent. (3.4% = 0.1 *M*.) This is needlessly high for the detection of K^+ in the concentrations (0.1 *M*) normally found in student unknowns. The solubility product at 25°C of $K(C_6H_5)_4B$ is 3×10^{-8} (*14*). Using one drop of 0.1 *M* reagent in five drops of test solution, one could theoretically detect about 10^{-6} *M* K^+. Probably because of supersaturation, neutral solutions containing less than 10^{-4} *M* K^+ were found to give no observable precipitate with 0.1 *M* reagent. This is in qualitative agreement with the sensitivity determinations reported by Amin (*9*), Crane (*10*), and Geilmann and Gebauhr (*15*). Concentrations of K^+ of the order of 10^{-4} *M* are often found in student unknowns as the result of traces of K^+ in reagents, or possibly from storage in soft glass reagent bottles. A number of Reagent Grade chemicals were found to give definite tests for K^+ using 0.1 *M* reagent.

The optimum concentration of reagent for present purposes was found to be 0.005 *M*. A curdy precipitate is obtained by using a more concentrated reagent, but with the 0.005 *M* reagent the result is a finely divided precipitate which is slow to settle. The sensitivity of the 0.005 *M* reagent is about 10^{-2} *M* K^+ in neutral solution which is equivalent to a dilution limit of about $1:2.5 \times 10^3$. The sensitivity appears to be considerably greater in NaOH of the concentration specified in the procedure below. Experience has shown that 0.005 *M* reagent will give a definite test for K^+ when present in student unknowns at a concentration of 0.1 *M*, but will not detect the traces of K^+ commonly found in such unknowns. A further advantage of

using these very dilute solutions of the reagent is that the cost is reduced to a negligible figure.

The reagent was prepared by dissolving in distilled water a weighed amount of solid $Na(C_6H_5)_4B$, which was purchased from the J. T. Baker Chemical Company. Some workers (*16*) advocate clarifying the reagent by addition of $AlCl_3$ which coagulates any $K(C_6H_5)_4B$ which may result from impurities and allows it to be filtered easily and quickly. Since no turbidity was observed when 0.005 *M* solutions of the reagent were prepared, it was not felt necessary to add any $AlCl_3$. The reagent is unstable in acidic solutions (*17*). The addition of $AlCl_3$ makes the solution acidic by hydrolysis, and it is necessary to adjust the *p*H to about 8 with NaOH in order to obtain adequate storage stability (*18*). Water solutions of the reagent alone are sufficiently alkaline to be stable at room temperature for several weeks. Decomposition eventually occurs through various intermediates to give benzene as one of the products. A strong odor of benzene is observed from solutions of the reagent which have partially or completely decomposed.

The following cations have been found to form precipitates with 0.005 *M* reagent: Ag^+, Hg_2^{+2}, Hg^{+2}, and NH_4^+. A number of other cations, which do not appear in the usual schemes of cation analysis, have been reported to form insoluble compounds with the reagent. These cations are Tl^+ (*19*, *20*, *21*, *22*), Ce^{+4} (*20*), Cu^+ (*20*), Rb^+ (*3*), and Cs^+ (*3*). Using 0.005 *M* reagent, no interference was found with Pb^{+2}, As^{+3}, Sb^{+3}, Sn^{+2}, Sn^{+4}, Bi^{+3}, Cu^{+2}, Cd^{+2}, Co^{+2}, Ni^{+2}, Al^{+3}, Cr^{+3}, Zn^{+2}, Fe^{+2}, Fe^{+3}, Mn^{+2}, Ca^{+2}, Ba^{+2}, Mg^{+2}, Sr^{+2}, Na^+, and Li^+, when the concentration of the above ions was 0.5 *M*. The following anions in concentrations of 0.5 *M* were found to give no interference using 0.005 *M* reagent: S^{-2}, $S_2O_3^{-2}$, SO_3^{-2}, SO_4^{-2}, ClO_4^-, ClO_3^-, ClO^-, BrO^-, IO_3^-, NO_2^-, NO_3^-, $C_2H_3O_2^-$, CO_3^{-2}, $C_2O_4^{-2}$, AsO_3^{-3}, AsO_4^{-3}, BO_3^{-3}, CN^-, SCN^-, CNO^-, $Fe(CN)_6^{-4}$, $Fe(CN)_6^{-3}$, PO_4^{-3}, CrO_3^{-2}, $Cr_2O_7^{-2}$, MnO_4^-, F^-, Cl^-, Br^-, and I^-. A number of organic alkaloids, amines, and quaternary ammonium salts have been reported to form precipitates with the reagent (*10*). Enough K^+ is present in some soapy water to give a test with 0.005 *M* reagent.

In analysis for K^+ in Group V, the only interference is from NH_4^+. However, $NH_4(C_6H_5)_4B$ can be distinguished from $K(C_6H_5)_4B$ by the fact that the former is soluble in warm NaOH while the latter is insoluble. If precipitation with $Na(C_6H_5)_4B$ is made in acid solution, and NaOH then added to determine whether the precipitate is $NH_4(C_6H_5)_4B$ or $K(C_6H_5)_4B$, Mg^{+2} and traces of other cations will form insoluble hydroxides with NaOH and lead to false conclusions regarding the presence of K^+. Therefore the most satisfactory procedure is to test for K^+ on the original solution after first removing all interfering ions with NaOH. The decantate can then be tested for K^+ by adding one or two drops of $Na(C_6H_5)_4B$. In strongly alkaline solution $NH_4(C_6H_5)_4B$ does not precipitate, even when allowed to stand in a closed container for a period of several weeks. Concentrations of NH_4^+ as great as 1.0 *M* do not interfere with the test for K^+ using the procedure described below.

The following procedure has been tested by the 120 students in our sophomore course in qualitative analysis and found to be satisfactory.

To 5 drops of the original unknown solution add an equal volume of 3 *N* NaOH. Centrifuge and test for complete precipitation by adding one more drop of NaOH. Add two drops of 0.005 *M* $Na(C_6H_5)_4B$. If K^+ is present a white precipitate forms immediately.

It has been found that 6 *N* NaOH prepared from a C.P. reagent gives a precipitate with 0.005 *M* $Na(C_6H_5)_4B$. Even with 3 *N* NaOH a very slight turbidity is sometimes observed, depending on the source of the NaOH. Since the NaOH is actually diluted to 1.5 *N* after the test for K^+ is completed, the use of 3 *N* NaOH should cause no interference with the test. However in order to verify this assumption, it is recommended that a blank be run on the NaOH supplied for the test.

Using the above procedure, results for K^+ in student unknowns have improved considerably. The test is far superior to both the cobaltinitrite test and the flame test, particularly if large amounts of sodium are present.

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An Evaluation of Reagents for Sulfide Precipitation

The comparative efficiencies of four sulfide-precipitating reagents: hydrogen sulfide, ammonium hydrosulfide solution, sodium hydrosulphide solution, and triethylamine hydrosulfide solution have been evaluated. The qualitative analysis Group II cations, arsenic(III), bismuth(III), cadmium(II), and copper(II), were precipitated and separated at 1.0 *M* hydrogen ion concentration by each reagent. Certain of the Group III cations, i.e., cobalt(II), manganese(II), nickel(II), and zinc(II), were precipitated in the presence of 5–6 millimoles of ammonia. Hydrogen sulfide was used also in precipitations and separations at 0.3 *M* hydrogen ion concentration because this *p*H is classical and specified by many texts in the separation of aluminum-iron group cations from the copper-arsenic group sulfides. Ammonium hydrosulfide, NH_4HS, was chosen as a reagent in preference to ammonium sulfide, $(NH_4)_2S$, because of the stability shown by the ammonium hydrosulfide solution. After precipitation of the sulfide, quantitative recoveries of each of the cations were made in accordance with recognized gravimetric methods. The reagents used were as follows:

Hydrogen Sulfide. The H_2S gas was passed through a column of anhydrous calcium chloride, then through a 2-liter flask of glass wool, before use. *Ammonium Hydrosulfide Reagent.* Dry H_2S gas was passed into iced (5°C) 3 *N* NH_4OH until the H_2S was no longer absorbed. *Sodium Hydrosulfide Reagent.* The preparation was identical to that of ammonium hydrosulfide solution, except that 2 *M* NaOH was used. *Triethylamine Hydrosulfide.* The triethylamine hydrosulfide solution first used in these experiments was made by a modification of the method of Achterhoff.[3] The reagent was prepared by a two-phase continuous extraction in which the cold triethylamine-ether phase was stirred mechanically in contact with the water layer into which the H_2S was passed. Ether extraction of the resulting triethylamine hydrosulfide solution separated a small amount of the unreacted base.

The 1.0 *M* hydrogen ion concentration was studied quantitatively because it was found that good separation of the aluminum-iron group cations is made from the precipitated copper-arsenic group sulfides at this acidity with triethylamine hydrosulfide reagent. The acidity in solution was established by 0.6 *N* or 2.0 *N* hydrochloric acid. Also, the total base, both combined and free, present in the precipitating reagent was neutralized by adding the equivalent amount of standard acid to the reaction mixture.

Each sulfide was precipitated with an excess of precipitant at room temperature (25–32°C) and at one atmosphere pressure. H_2S was used in very large excess as is customary. A moderate stoichiometric excess of approximately 50 to 300% of the ammonium, sodium, or triethylamine hydrosulfide reagent was employed. The excess of each of these reagents was decomposed by an equivalent quantity of standard hydrochloric acid solution, forming H_2S. The H_2S concentration of the solution above the Group II sulfides varied from 0.012 to 0.065 *M*, using ammonium hydrosulfide; from 0.008 to 0.026 *M* with sodium hydrosulfide; and from 0.016 to 0.045 *M* for triethylamine hydrosulfide reagent. The H_2S concentration of the solution above cadmium sulfide was 0.026 *M* using sodium hydrosulfide, 0.030 *M* with ammonium hydrosulfide, and 0.041 *M* for triethylamine hydrosulfide reagent.

In the analytical practice, equilibrium was accomplished by allowing the precipitated sulfide to stand for 1 hour in contact with its supernatant solution in an open beaker.

Precipitation of cadmium sulfide at 1.0 *M* hydrogen ion concentration was nearly complete. The precipitation of cadmium ion as cadmium sulfide was found to be 97% with hydrogen sulfide, 93.4% with ammonium hydrosulfide, 93.8% by sodium hydrosulfide, and 95.6% by triethylamine hydrosulfide reagent. The calculated cadmium ion concentration in equilibrium with cadium sulfide is 1.3×10^{-5} *M*. The cadmium ion concentration found in 1.0 *M* hydrogen ion solution was 4.3–7.8×10^{-4} *M*. Precipitation of arsenic(III), bismuth(III), cadmium(II), and copper(II) ions is total at 0.3 *M* hydrogen ion concentration.

Co-precipitation of cobalt(II) and nickel(II) sulfides at 1.0 *M* hydrogen ion concentration is negligible at the low concentrations used in the quantitative precipitations. However, in the more concentrated solutions from which the copper-arsenic group cations are precipitated qualitatively with the ammonium hydrosulfide or with the triethylamine hydrosulfide reagent, a modest amount (2–5 mg) of cobalt(II) sulfide and or nickel(II) sulfide usually is co-precipitated. In the qualitative tests, the original ion concentration is 0.10 to 0.15 *M*.

Nickel ion was not precipitated with sodium hydrosulfide reagent. A colloidal brown solution was formed from which no nickel sulfide could be separated. To a modest extent the same phenomenon was observed in the case of ammonium hydrosulfide reagent. Centrifuging improved, but did not complete, the separation. Evidently, the presence of a small concentration of polysulfide in the reagent solution causes the formation of colloidal nickel sulfide.

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[3] Achterhoff, M., Conway, R. F., and Boord, C. E., *J. Am. Chem. Soc.*, **53**, 2682 (1931).

Conclusions

Ammonium hydrosulfide, NH_4HS, and triethylamine hydrosulfide reagents are equally convenient, prompt, and efficient in precipitating the cation sulfides, except that the ammonium hydrosulfide permits a small amount of nickel ion to remain in solution as colloidal nickel sulfide. Either reagent can be used in the same qualitative method. Both reagents show good stability to oxidation by the air.

Separation of the Group II (copper-arsenic) sulfides from the Group III (aluminum-iron) ions is effective at 1.0 *M* hydrogen ion concentration. A trace of cadmium ion may remain in solution after the Group II precipitation but does not interfere in subsequent separations and identifications.

Co-precipitation is negligible at the low ion concentrations employed in the quantitative recoveries. Precipitation of the Group II cations from the more concentrated solutions of the ions usually results in the co-precipitation of a modest amount of cobalt(II) and nickel(II) sulfides.

Sodium hydrosulfide is an excellent precipitating reagent for many cations.

Acknowledgment

The authors are indebted to Dr. E. B. Middleton for the idea of using triethylamine hydrosulfide reagent in a course of qualitative analysis. Triethylamine hydrosulfide reagent has been used for five years at A. and M. College of Texas. John Hill showed that the sulfides of the copper-arsenic and aluminum-iron groups could be precipitated by triethylamine hydrosulfide.

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The Preparation of Barium Chloranilate

The use of barium chloranilate in the colorimetric determination of sulfate[1] offers an effective means of introducing classes in quantitative analysis to indirect, colorimetric procedures, although the cost of reagents is somewhat excessive if large classes are to be accommodated. A reagent of sufficient quality may be prepared easily and economically by precipitating barium chloranilate from a solution of chloranilic acid (Eastman P-4539) with barium hydroxide. While chloranilic acid is only slightly soluble in water at room temperature, it is soluble to the extent of 14 g per l at 99°C, and the addition of acetone renders it considerably more soluble at elevated temperatures.

To 16 grams of chloranilic acid in a 3-l beaker, add about 700 ml of water and 300 ml of acetone and heat until the acid has dissolved. While the hot solution is stirred vigorously, add a hot, freshly-filtered barium hydroxide solution (20 g per l), until the purplish-red color of the solution diminishes in intensity to a pink color. One should not carry the addition of the barium hydroxide solution to the equivalence point. Overshooting this point allows the excess of barium ions to be adsorbed on the precipitated chloranilate. If one does overshoot this point, more of the chloranilic acid, dissolved in acetone, may be added until a decidedly pink color of the supernatant liquid is obtained. A tan, somewhat curdy precipitate is formed initially which changes into a dense, purplish–brown crystalline material upon aging, as described by Bertolacini and Barney. Allow to stand overnight, decant the supernatant liquid and wash the crystals free of the excess chloranilic acid with several portions of water to which equal volumes of ethanol have been added. The yield is nearly theoretical, depending upon how closely one approaches the equivalence point in the addition of the barium hydroxide.

In the analysis laboratory the procedure recommended by Bertolacini and Barney is followed. Soluble sulfates, free of interfering ions and containing between 1 and 20% SO_3, are used as unknowns. A 1.0-g sample of unknown is dissolved in water, adjusted to approximately *p*H 4 with dilute HCl (methyl orange paper), and diluted to 250 ml in a volumetric flask. A 10-ml aliquot of this solution, 10 ml of a buffer solution (0.05 *M* potassium acid phthalate), and 25 ml of 95% alcohol are placed in a 50-ml volumetric flask and diluted to the mark with water. A 0.20-g portion of the solid barium chloranilate is added and the mixture shaken at intervals for 15 minutes. The solution is filtered through a double filter paper and compared in a spectrophotometer at 530 mμ with a blank prepared in the same manner. The calibration curve is prepared by treating definite volumes of an ammonium sulfate solution (1.645 g $(NH_4)_2SO_4$ per l or 1 mg SO_3 per ml) as described above and comparing with a blank.

[1] Bertolacini, R. J., and Barney, J. E., *Anal. Chem.*, **29**, 281-83 (1957).

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The Separation of Arsenic in Qualitative Analysis

A separation of arsenic as As(III) has been developed based upon the observation that As(III) is extracted selectively from hydrochloric acid solutions of the common cations encountered in the usual qualitative analysis scheme. The extraction is effected by a saturated solution of catechol in benzene.

To 6–8 drops of the unknown contained in a small beaker, add 2 drops of 4 *M* NH_4Cl and evaporate to dryness carefully. Extract the residue with 6–8 drops of 6 *M* HCl, decant if necessary, and add 1–2 drops of 0.25 *M* NH_4I. Warm the solution on a water bath until there is no further liberation of free iodine. Transfer to a 4-ml test tube, add an equal volume of a saturated solution of catechol in benzene, and extract by shaking the mixture for three minutes. Centrifuge the mixture and separate by withdrawing the benzene layer with a pipet. Saturate the benzene extract with H_2S. A precipitate of greenish yellow As_2S_3 which tends to adhere to the glass confirms the presence of arsenic.

Experiments have shown that Cu(II) and Fe(III) will interfere with the reduction step in the test as described above. The interference of Cu(II) can be avoided if 2–3 drops of 0.25 *M* $SnCl_2$ are substituted for the NH_4I normally used in the test. Fe(III) can be eliminated from the unknown by precipitation with base.

It is possible to use $SnCl_2$ as the reducing agent in the place of NH_4I except in the presence of mercury in the unknown. Moreover, the danger of reducing As(V) to elementary arsenic exists when $SnCl_2$ is utilized.

By this procedure it is possible to detect as little as 20 micrograms of arsenic. This is a much lower concentration of arsenic than is normally encountered by the student.

An estimated value of the distribution coefficient for As(III) between 6 *M* HCl and a saturated solution of catechol in benzene is 0.92. This indicates the possible application of the extraction technique to the quantitative estimation of As(III) by counter-current extraction or merely employing repeated extractions in the absence of counter-current extraction apparatus.

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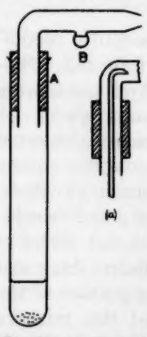
A Gas Testing Device Using Liquids or Test Papers

Although tests for gases evolved during small-scale qualitative inorganic analysis are often made with a drop of reagent supported on the end of a glass rod, results are uncertain in the hands of beginners or when the concentration of gas is not high. The gas testing device shown in the figure is more satisfactory and may be constructed in a few minutes from 6-mm outside diameter glass tubing. Rubber tubing sleeve *A* enables the device to be inserted directly into the mouth of the 10-mm diameter semimicro test tube from which the gas is to be evolved. By means of a fine-tipped test pipet, 0.05 to 0.1 ml of a suitable reagent is introduced into bulb *B* and the appearance of the reagent is observed as the gas flows over its surface.



Simple gas-testing device.

Apart from its use with liquid reagents such as lime water, mixed bromine and barium chloride solutions, etc.,[1] the device will hold narrow starch-iodide, *p*H-sensitive, and other test papers. Even dry papers are amply supported if thrust in far enough to enter the bend, as shown at (*a*).

Where deleterious to a test being carried out with a liquid reagent, spray carried up from the reaction mixture may be largely arrested by using a lightly-twisted narrow strip of filter paper in place of impregnated paper. Although to be used with caution owing to possible attack upon the central wire, a 30-mm length of pipe cleaner is a more efficient trap. This is pushed around the bend until the inner end is a few mm from the bulb.

When wetted with a suitable absorbent, the pipe cleaner trap will qualitatively remove components of certain gas mixtures. Thus after absorption of carbon dioxide with sodium hydroxide solution, the carbon monoxide also evolved during the dehydration of an oxalate by concentrated sulfuric acid may be readily ignited at the outlet of the gas testing device.

[1] Stock, J. T., and Heath, P., "Small-scale Inorganic Qualitative Analysis," Chemical Publishing Company, New York, 1954.

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Oxidation of Hydrogen Sulfide in Inorganic Qualitative Analysis

In acid solution, hydrogen sulfide is readily attacked by oxidizing agents. Sulfur deposition and possible formation of sulfate ion are the results most significant in the usual scheme of qualitative analysis. Although sulfur deposition may confuse beginners, this phenomenon is rarely serious if suitable techniques are employed. Sulfate formation is far more insidious, since partial or complete precipitation of the members of the alkaline earth group may then occur prematurely. This has led to the recommendation that alkaline earth cations should be separated immediately after the silver group (*1*).

Oxidizing agents commonly encountered in introductory qualitative analysis are nitrate, ferric salts, chromate or dichromate, and arsenate; less usual are permanganate, chlorate, and other oxyhalogen anions. Although 30 years have elapsed since it was shown that 5% nitric acid does not attack hydrogen sulfide (*2*), the statement that the presence of nitrate causes sulfate formation may be found in modern texts. Golovanov studied the effect of hydrogen sulfide on dilute nitric acid solutions containing cations of the first three groups and found that sulfate formation did not occur (*3*).

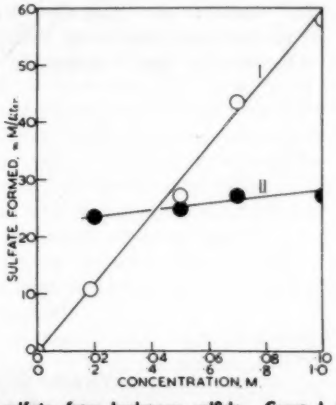
To examine the sulfate-forming tendencies of various oxidizing agents, 0.05 *M* solutions of each of these in turn were prepared in 1 *M* hydrochloric acid. Triplicate 100-ml portions of each solution were heated to incipient boiling, when hydrogen sulfide was bubbled through for about 10 minutes without further heating. After again boiling to eliminate hydrogen sulfide and to coagulate liberated sulfur, the mixtures were filtered and the sulfate in each was determined by precipitation as barium sulfate. Average results were as follows:

Agent	$SO_4^=$ found, in mM/l
Nitric acid	0.0
Ferric chloride	1.0
Potassium dichromate	27.2
Sodium arsenate[a]	1.9
Potassium permanganate[b]	6.8

[a] 0.1 g of ammonium iodide added as reduction catalyst.
[b] Destroyed by hot acid; agent is presumably residual chlorine.

Dichromate is thus outstanding in its tendency to cause sulfate formation; this conclusion is not altered if the differing molar oxidizing capacites of the agents are taken into account.

Further experiments were made with 100-ml portions of 1 *M* hydrochloric acid containing various concentrations of dichromate. Despite precautions for sulfate determination in the presence of chromic salts (*4*), replicates showed considerable scatter, especially at low dichromate concentrations. This may be largely due to non-identical temperature conditions during the runs. Average data are indicated by curve I in the figure; each mole of dichromate may thus cause the



Formation of sulfate from hydrogen sulfide. Curve I (upper scale), variable $[Cr_2O_7^{-2}]$ in 1 M HCl; II (lower scale), variable [HCl] containing 0.05 M $Cr_2O_7^{-2}$.

premature precipitation as sulfate of about 0.6 mole of barium, etc. As indicated by curve II, the effect is but slightly diminished by reducing the concentration of hydrochloric acid.

Dichromate may be readily reduced by heating with dilute hydrochloric acid and ethanol (*5*) or, less conveniently, by evaporating with concentrated hydrochloric acid or acidified hydrogen peroxide. Such pretreatments do not, however, reduce the milder oxidizing agents such as ferric salts. Sulfur deposition may then still occur on subsequent treatment of the "unknown" solution with hydrogen sulfide. In practice, therefore, it is often simpler to omit pretreatment of oxidizing agents and to destroy them by ample treatment with hydrogen sulfide. On the semimicro scale, examination of the precipitate for members of the copper-arsenic group is rapid and not easily confused by the presence of free sulfur (*6*).

Any dichromate left unreduced will not, of course, precipitate as chromic hydroxide when the solution is rendered ammoniacal. Instead, it is conceivable that the iron group precipitate may contain the water-insoluble chromates of members of later groups. The speed of reduction by hydrogen sulfide of 4-ml portions of hot 0.05 *M* dichromate was therefore investigated in the acidity range 0.2 to 1 *M*. After treatment with hydrogen sulfide for a given time, the solution was boiled to expel excess gas, cooled, and treated with 1 ml of 0.05 *M* ferrous sulfate solution. Excess of the latter

This work was carried out with the partial support of the United States Atomic Energy Commission.

was then back titrated with 0.01 *M* dichromate solution. These experiments showed that destruction of dichromate was virtually complete 3 minutes after introduction of hydrogen sulfide and slowness of saturation with the gas was probably a limiting factor. Experiments were, therefore, repeated with 0.5-ml portions of solution; these may be rapidly saturated without wastage of hydrogen sulfide by use of a simple attachment and an agitation technique (*6*). The results showed that most of the dichromate is destroyed after treatment for one minute. It is therefore recommended that the hot acidified solution should be saturated with hydrogen sulfide and, with the attachment still in the mouth of the 75-× 10-mm test tube, the mixture should be allowed to stand for 3 to 5 minutes before centrifuging. This allows time not only for reduction of oxidizing agents but also for the proper separation of the sulfides of the copper-arsenic group.

Only in the simultaneous presence of chromate or dichromate and barium, etc. (usually obvious after completion of preliminary and anion tests), may the smallness of the alkaline earth carbonate precipitate hinder its examination. In such cases, barium, etc., may be separated as sulfates before use of hydrogen sulfate (*1*). The sulfates may be got into solution either by a sodium carbonate of similar fusion or by conversion to chlorides by heating with sulfuric acid and excess thionyl chloride (*7*).

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Detection of Thiocyanate and Dissolution of Silver Halides

It is frequently desirable in qualitative analysis to separate as an insoluble silver group precipitate the following anions: SCN^-, Cl^-, I^-, Br^-. The presence of large amounts of CNS^-, and/or I^- may produce interference with the usual subsequent individual tests as follows: (*a*) Large amounts of I^- may interfere with the detection of SCN^- in that I^- reacts with Fe^{+3} to liberate free iodine which masks the iron-thiocyanate color.

$$Fe^{+3} + I^- \rightleftharpoons Fe^{+2} + {}^1/_2\, I_2$$

(*b*) Large amounts of SCN^- may interfere with the halide tests based on the differential oxidation of these anions to produce free halogen. The red color of the iron-thiocyante complex may mask the detection of small quantities of iodine which have been extracted into chloroform. The SCN^- may also be oxidized to CN^- which may then react with iodine or bromine to produce volatile iodo- or bromocyanogen.

Since the decomposition products of sodium formate react with SCN^- with the formation of CN^- and S^- and also dissolve the silver halides, it was suggested that this reagent be incorporated into the group analysis scheme.[1] The chemical reactions are as follows:

$$2HCO_2Na \rightarrow Na_2CO_3 + CO + H_2$$

$$2AgHalide + Na_2CO_3 + H_2 \rightarrow 2Ag^0 + 2NaHalide + CO_2 + H_2O$$

$$2AgSCN + 3Na_2CO_3 + 3H_2 \rightarrow 2Ag^0 + 2NaCN + 3H_2O + 3CO_2 + 2Na_2S$$

The NaCN and Na_2S are partially hydrolyzed, and the H_2S produced may be detected in the usual manner.

To a sample solution in a test tube or porcelain crucible from which S^{-2}, CN^-, $Fe(CN)_6^{-3}$, $Fe(CN)_6^{-4}$, $S_2O_3^{-2}$, and SO_3^{-2} have been removed, add $AgNO_3$ to form the group precipitate containing AgSCN, AgI, AgBr, and AgCl. Wash the precipitate thoroughly. Add approximately twice the precipitate's weight of sodium formate, and heat slightly above 400°C. Place a piece of paper moistened with a solution of lead acetate over the mouth of the test tube or crucible. The formation of lead sulfide on the paper indicates the presence of thiocyanate in the sample solution. Continue heating until the formate is completely decomposed and the volatile products are driven off. Cool the reaction vessel, add water, and filter the suspension or use a centrifuge. The clear solution contains the sodium salts of the halides. Make this solution acidic with 6 *N* acetic acid. Apply heat, and test again for complete removal of the hydrogen sulfide. Any of the accepted procedures for the halides may then be applied to this solution.

This procedure will detect the presence of 1 mg of I^-, Br^-, Cl^-, or SCN^- in any mixture containing up to 100 mg of each of the other ions.

[1] Caldas, A., and Gentil, V., J. Chem. Educ., **35**, 545 (1958)

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Qualitative Analysis in the General Chemistry Program

There is an increasing tendency to include qualitative analysis in the general chemistry program. We believe this trend is in the right direction provided qualitative analysis is integrated in the course as a means of teaching the principles of ionic equilibrium and of developing considerable initiative and resourcefulness in the laboratory. Our experience has shown that the practice of having students work out their own analytical procedures is a highly successful one, not only for teaching the properties of the ions and the principles involved in the analytical separations, but also for keeping the laboratory work from becoming mere routine. Furthermore, student interest is maintained at an unusually high level.

Our students develop semi-macro tests for eight common anions, together with procedures to be followed when testing in the presence of possible interfering ions. The semi-macro schemes for the analysis of the usual number of cations are worked out after completion of tests which enable the student to fill in a flow sheet for the precipitation, separation, and identification of the cations in the various groups.

We believe teachers generally will agree that the procedure described has many pedagogic advantages. Some instructors, however, may fear that the average freshman is not capable of working out his own scheme of analysis without considerable individual attention and without requiring more time than is usually available. Others may feel that the analytical results will not compare favorably with those obtained by students using conventional directions.

We have recently completed a study of the analytical results obtained by 256 "run-of-the-mill" students who worked out their own analytical procedures. The percentages of ions reported both correctly and incorrectly by our students were generally as good or better than those reported by several authors in THIS JOURNAL for analyses made by students using conventional methods. Furthermore, the laboratory time required has been found to be approximately the same as that used by students who perform an equivalent number of the preliminary experiments given in many manuals prior to the directions for the analytical procedures. One instructor has been in charge of each section of approximately 24 students.

We are convinced that the program described is valuable in helping to keep the freshman laboratory work from becoming "cook-book" chemistry, and for giving more than the usual amount of training in learning to think independently and critically.

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Separating Copper from Cadmium Without Cyanide

The procedure here suggested is based on the observation that CdS is soluble in hot dilute H_2SO_4, whereas CuS is insoluble. Therefore, after passing H_2S into a mixture of Cu^{++} and Cd^{++} salts in HCl, we get precipitate of both CuS and CdS. This is filtered and the precipitate is boiled for two to three minutes with dilute H_2SO_4 and filtered. The residue is CuS and the filtrate now contains Cd^{++}. If, into this filtrate, H_2S gas is passed, we get a heavy orange precipitate of CdS. If the filtrate is then neutralized with NH_4OH, after which it is acidified with dilute hydrochloric acid and finally saturated again with H_2S, we then get the conventional canary yellow precipitate of CdS.

Spot Test

This method can be utilized for a spot test. When a drop or two of a solution of Cu^{++} and Cd^{++} salts in HCl are taken on a filter paper and H_2S is passed over them, the spot becomes deep black. If a few drops of boiling dilute H_2SO_4 are added, a ring is formed on the paper around the spot. If H_2S is passed over the filter paper the moistened ring becomes yellow due to the formation of CdS.

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A Pharmaceutial Analysis Experiment for General Chemistry Laboratory

Many laboratory programs in general chemistry include at least one experiment in volumetric acid-base determinations, and a part of this experiment often involves the determination of the concentration of an acetic acid (vinegar) solution. Several years ago, in order to make this experiment of more general interest for both student and instructor, aspirin tablets were issued and the aspirin content determined by titration with standard base. These tablets are readily available with aspirin content ranging from 65 mg (1 grain) to 455 mg (7 grains), and they are made in various colors. Materials such as starch, lactose, and stearates used in preparation of the tablets do not interfere with the analysis. Tablets that contain acetophenetidin (phenacetin) and caffeine in addition to the aspirin can be included in the list of "unknowns," since these two substances do not react during the titration. The variation from average tablet weight is seldom more than ± 1%, and since the amount of aspirin *per tablet* is to be determined, no weighing operations are required.

The encouraging student reaction to the aspirin determination led us to design an experiment involving (1) the identification of the active acidic component in a pharmaceutical tablet, and (2) the determination of the amount of this acidic substance present. Tablets containing the following substances were issued for analysis: aspirin, *p*-aminosalicylic acid, ascorbic acid (vitamin C), quinidine sulfate, thiamine hydrochloride (vitamin B_1), phenobarbital, and sulfathiazole. Other acidic substances, such as nicotinic acid, might be added to this list.

Qualitative Analysis Experiments

The following qualitative identification tests should be demonstrated by the instructor at the beginning of the laboratory period: Place two of the tablets in the center of a piece of filter paper. Wrap and fold so that the tablets are covered by several layers of paper; then crush them with a spatula as completely as possible. In case the tablets are extremely small it is advisable to use three or four at this point. Use the spatula to divide the powdered material into five approximately equal portions on the paper and use one portion for each of the following tests.

(*A*) *Aspirin and p-Aminosalicylic Acid.* Introduce a portion of the material into a 15-ml test tube, add 10 ml of water, and heat gently. Tablets containing aspirin generally disperse readily and dissolve almost completely in less than one minute. It is helpful to leave a small stirring rod in the test tube during the heating process. Constant agitation to the tube while heating will cause vibration of the rod and help to mix the material.

Allow the mixture to cool for a few seconds and add 3 or 4 drops of $FeCl_3$ solution. The development of a definite purple color establishes the presence of aspirin (*1*). The development of a reddish-brown color with a slight purple character is evidence of the presence of *p*-aminosalicylic acid (*2*). These two compounds are very easy to identify by this test and no difficulty should be encountered.

(*B*) *Ascorbic Acid.* Introduce a portion of the material into a test tube and add 5 ml of $CuSO_4$ solution (0.1 *M* aqueous). Stir thoroughly and place the tube in a beaker of hot water. If ascorbic acid is present, a fine orange colored precipitate of Cu_2O will form in less than five minutes. The solution will probably change during this time from a blue to green color. It is possible that tests involving sodium nitroprusside (*3*) or methylene blue would be equally satisfactory.

(*C*) *Quinidine Sulfate.* Place a portion of material in a test tube, add 5 ml of dilute H_2SO_4, and heat to disperse. Cool the tube under running water for a few minutes and then examine for fluorescence. If a distinct blue fluorescence develops, the presence of quinidine sulfate is to be concluded (*4*).

A small ultraviolet source will make this observation very striking. A test tube containing quinidine sulfate solution and another containing a material that is not fluorescent may be used for comparative purposes.

(*D*) *Sulfathiazole.* In case no fluorescence develops, cool the acidified material from (*C*) in ice, add 3 ml of sodium nitrite solution (1 *M* aqueous) and mix the contents of the tube thoroughly. A small amount of oxides of nitrogen will be liberated at this point due to partial decomposition of nitrous acid. The instructor may advise making this test in the hood since these oxides are toxic and corrosive. Add to the top of the solution, without mixing, 5 or 6 drops of beta-naphthol solution. The development of an orange-brown layer at the top indicates the presence of sulfathiazole (*5*).

(*E*) *Thiamine Hydrochloride.* Place a portion of material in a test tube, add 5 ml of water, and warm gently for about one minute. Add 5 or 6 drops of a mixture of $FeCl_3$ and $K_3Fe(CN)_6$ (freshly prepared mixture of equal volumes of 0.1 *M* aqueous $FeCl_3$ and $K_3Fe(CN)_6$ solutions), and allow to stand for about five minutes. The development of a green color, changing to blue, shows the presence of thiamine hydrochloride (*6*). The change in color will be slow and gradual. It will be helpful to prepare a blank for comparative purposes by placing 5 ml of water in a second tube, adding 5 or 6 drops of the prepared reagent, and allowing the two tubes to stand side by side.

An alternate but more elaborate test involves oxidation of the vitamin and observation of fluorescence (*7*).

(*F*) *Phenobarbital.* Place a portion of material in a dry test tube, add about 5 ml of chloroform, and shake the mixture vigorously for about one minute. Add 1 ml of $Co(NO_3)_2$ solution (0.05 *M* in methanol) and 3 ml of isopropyl amine solution (1 *M* in methanol) and mix thoroughly. The development of a bright purple color indicates the presence of phenobarbital (*8*).

These tests are based on the reducing properties of certain of the compounds, (*B*) and (*E*); the formation of colored complexes, (*A*) and (*F*); and diazotization (*D*). The tests are very useful even though in some cases the exact chemical changes involved may not be completely clear. They are specific, of course, only when applied to the compounds described in this experiment and in the order assigned.

Presented before the Division of Chemical Education at the 133rd Meeting of the American Chemical Society, San Francisco, April, 1958.

Quantitative Analysis Experiments

One tablet is dispersed in 75 ml of solvent (water or 50% aqueous alcohol) in a 250-ml Erlenmeyer flask. It is then titrated with 0.1 *N* sodium hydroxide, using phenolphthalein as the indicator. In case an alcoholic solvent is desired it may be prepared from methyl, ethyl, propyl, or isopropyl alcohol. If the volume of alkali required to titrate one tablet is less than 5 ml it will be best to use two tablets for subsequent titrations. The first titration may be made rapidly for exploratory purposes, and a second and third titration made carefully as possible. The titration is carried to the point where the pink color of the indicator persists for at least 15 seconds.

Specific instructions, where necessary, for titrating the individual substances are as follows:

(*A*) ***Aspirin.*** The alcohol-water solvent is used. Hold the flask by its neck and warm the contents slightly by heating in a small flame. Do not heat beyond the point where the bottom of the flask can be held in the palm of the hand without discomfort. The tablets may then be dispersed readily by crushing with a glass rod and by swirling.

(*B*) ***p-Aminosalicylic Acid.*** Quinidine Sulfate. Phenobarbital. Sulfathiazole. Follow the same procedure described in paragraph (*A*) except that the solvent may be heated almost to boiling, if necessary, to facilitate disintegration of the tablets. The titration can be carried out on the warm solution.

(*C*) ***Ascorbic Acid.*** Water is used as the solvent and the material must not be heated. The pink indicator color will fade after the end point is reached but the color persists for at least 10–15 seconds. If the solution is cooled below 10° C just before titration the color is more stable.

(*D*) ***Thiamine Hydrochloride.*** The tablets are broken up in water with the aid of a stirring rod. The resulting suspension is cooled in ice to a temperature below 10°C just before titrating. The indicator color fades but is stable for at least 30 seconds.

Student Results

The results of approximately 400 analyses are summarized in the Table. The determinations were made by general chemistry laboratory classes composed of science majors, engineers, and liberal arts majors. Any determination that exceeded ± 10 in average deviation was assumed to involve gross technical or mathematical carelessness and was not included. The number of results thus rejected was less than 10%.

Analysis of Pharmaceutical Tablets

Compound	Color[b]	Stated content Mg	Av calc content Mg	Av dev	Range Mg	Number of detns
Phenobarbital	W	49	52	±0.9	50–54	6
Phenobarbital	W	65	69	±1.4	67–72	9
Phenobarbital	W	97	101	±2.1	98–107	13
Phenobarbital	Y	97	104	±3.1	98–110	11
Thiamine hydrochloride	W	50	57	±3.2	48–65	18
Thiamine hydrochloride	W	100	113	±3.5	103–121	49
p-Aminosalicylic acid	W	500	498	±5.5	481–509	39
Quinidine sulfate	W	194	203	±4.4	191–215	41
Sulfathiazole	W	500	507	±5.2	493–517	35
Aspirin	W	65	70	±1.6	66–74	8
Aspirin[a]	W	227	233	±3.5	225–245	33
Aspirin[a]	P	227	234	±3.9	225–241	8
Aspirin[a]	Y	227	234	±6.0	218–245	13
Aspirin	W	324	337	±5.7	326–345	23
Aspirin[a]	G	324	340	±7.0	328–353	22
Aspirin	Y	324	331	±3.9	324–341	10
Aspirin[a]	W	454	459	±4.8	442–471	45

[a] Contained acetophenetidine and caffeine.
[b] W white, Y yellow, P pink, G green.

The results shown in the table indicate that in practically all analyses the experimental results were high. This is to be expected since the mixtures being titrated will be cloudy in appearance and will require one or two extra drops of alkali to produce a convincing indicator color change. In some cases the manufacturer will introduce a slight excess of active material, and this is particularly true in the case of vitamins. Aspirin, of course, will undergo some hydrolysis during the titration. Official tolerances for most of these substances will average about 95–105 % of the stated amount except for the vitamins, where the tolerance will be of the order of 95–115 %.

Materials for this experiment were assembled at various times and represented different production runs. It was therefore impractical to make a control or check analysis on each material issued.

Sulfadiazine was included in the original experiment but the results are not reported. Due to its greater insolubility it is readily distinguished from sulfathiazole, but this insolubility causes the titration to be very tedious.

The procedure for analysis of ascorbic acid was worked out after the experiment had been completed, so ascorbic acid is not among the materials listed in the table.

The presence of colored materials in the tablets does not seriously obscure the indicator color change but does increase the average deviation appreciably.

It is readily admitted that the average student in general chemistry will not understand the nature of all the reactions used in the qualitative identification tests. Most of the tests are simple and reliable, however. The complete experiment is no longer used in general chemistry but it could be included in the laboratory program of organic chemistry or organic analysis —with a greater understanding on the part of the student. Certainly it is an experiment that is different from most and one that the student will find interesting.

It should be understood that these titrations are not official analytical procedures. In careful hands, however, these simplified procedures are capable of giving very good results.

Acknowledgment

We wish to thank the First Texas Chemical Manufacturing Company of Dallas, Texas, for supplying most of the materials used in this study.

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Toluene-3,4-Dithiol and Its Derivatives as Analytical Reagents

A new approach to qualitative inorganic analysis

Nineteenth century chemists employed a limited number of simple analytical techniques such as the flame-, borax bead, and charcoal-block tests. In 1905, Tschugaev discovered that dimethylglyoxime gave a red precipitate which was uniquely characteristic for the nickel ion. This was the first widely used organic spot-test reagent for a metal and, since that time, organic compounds have been used in inorganic analysis in bewildering profusion. This abundance of reagents has led to much confusion in the minds of beginning students. Thus they ask what determines which particular reagent should be used when confirming, say, bismuth or tin? Why? Exactly what chemical principles are involved? How do they operate? These and similar questions confound the beginner (and not infrequently the research chemist!) who concludes that inorganic analysis employing organic reagents is more an art than a science!

The purpose of this article is to show that these difficulties are readily overcome when analysis is thought of as a *unity*. The traditional basis of analysis is perfectly rational. Cations are divided into groups depending upon precipitation by hydrochloric acid, hydrogen sulfide in acid solution, ammonia in presence of ammonium salts, hydrogen sulfide in alkaline solution and ammonium carbonate. What is required is to relate the confirmations of each element to the basic scheme.

If we agree that organic reagents are desirable in inorganic analysis, a logical approach is to look for organic analogues of the Group precipitants, so that the thiophilic elements (those precipitated as insoluble sulfides) may be separated from those which are oxyphilic (those precipitated as insoluble hydrated oxides). Thus, a search is first made for organic analogues of hydrogen sulfide, which will precipitate the thiophilic elements. Secondly, a search is made for organic analogues of ammonium hydroxide, considered as a derivative of water, which will precipitate the oxyphilic elements.

Taking hydrogen sulfide first, the organic compound we look for will be:

(1) An aromatic compound since resonance in the ring will aid in the development of brilliant color. Further, aromatic compounds are only sparingly soluble in water.

(2) A compound with two —SH groups since, in H_2S, there are two acidic hydrogen atoms bonded to sulfur. As in the case of H_2S, aromatic SH-containing compounds are weak acids, the dissociations of which are dependent upon the *p*H of the solution.

(3) An aromatic compound containing two – SH groups in the ortho position, since these readily form stable, usually water-insoluble, chelates with metal cations.

Bearing the above points in mind the reagent of choice is seen to be benzene-1,2-dithiol. Unfortunately, this compound is difficult and expensive to make. Toluene-3,4-dithiol ("dithiol," DT), is readily available, not too expensive, and is extremely similar to hydrogen sulfide in its properties. Dithiol gives highly selective reactions for most of the metals which are precipitated by hydrogen sulfide. When dithiol fails, the structurally-similar, readily available, and more strongly acidic quinoxaline-2,3-dithiol (QDT) is employed. This is a valuable reagent for nickel and is superior to dimethylglyoxime.[4,5]

Table 1

Group	Element	Reagent used for confirmation	Concentrations necessary for good reactions (parts per million)
I	Ag	DT	5
	Hg	DT	50
	Pb	DT	5
IIA	Hg, Pb	As above	...
	Bi	DT	1
	Cu	DT	1
	Cd	H_2S	50
IIB	As	DT	1
	Sb	DT	50
	Sn	DT	1
III	Fe (Also precipitates in Group 4)	Catechol or DT	1, 1
	Cr	Catechol	50
	Al	Alizarin	...
IV	Co	DT	1
	Ni	QDT	1
	Mn	DT	1
	Zn	H_2S or DT	50, 50

Exactly similar logic leads to the choice of benzene-1,2-diol ("catechol") as the organic analogue of ammonium hydroxide. Two of the Group III metals (Cr and Fe) give characteristic reactions with catechol, but for aluminum the functionally similar alizarin is employed. Certain of the rarer Group III elements react with tannic acid or tannin, which is a catechol-like compound of higher molecular weight.

Remembering that Group I elements, which are usually precipitated as chlorides, are also precipitated as sulfides in acid solution it is not surprising that dithiol can be used to confirm them. Thus, confirmatory tests for the sixteen common elements in Groups I to IV become quite logical (Table 1).

[1] For reprints: 783 Cereza Drive, Palo Alto, Calif. This article appeared in a different form in *School Science Review*, **40**, No. 140, pp. 41–51 (1958).

Dithiol and Its Use

Since this article is about dithiol, which may be unfamiliar to some readers, we shall now describe its properties and the ways in which it is used. Dithiol is a colorless solid (mp 35°) possessing a characteristic, faint, but not unpleasant odor. Like hydrogen sulfide it is a mild reducing agent, though barely so in strong acid, and it is oxidized by atmospheric oxygen to the polymeric disulfide, $(C_7H_6S_2)_n$. When first precipitated this polymer resembles sulfur in appearance and, like sulfur, is soluble in carbon disulfide, but few other solvents.

Dithiol precipitates the same metals as does hydrogen sulfide and usually under similar conditions. Its derivatives, which in this article we shall refer to as *mercaptides*, are sometimes (as with Sn) less soluble than the sulfides, and sometimes (as with Pb) more soluble. Many sulfides (e.g., CuS and CoS) dissolve readily in an alkaline solution of dithiol. The mercaptides of Group IIB metals dissolve in alkali, whereas those of Group IIA are insoluble, although they may dissolve in an alkaline solution of dithiol. This latter phenomenon may be compared with that of the solubility of mercuric sulfide in alkaline sulfides.

The resemblance between hydrogen sulfide and dithiol extends to many other reactions. For example, both reagents give a positive nitroprusside reaction. Cobalt and nickel mercaptides, like the corresponding sulfides, fail to precipitate except in weak acid but, once precipitated, they are not dissolved except by a much stronger acid. Among the common cations arsenic is unique in the ease with which it gives colloidal solutions of arsenic mercaptide or sulfide. Without doubt, dithiol could replace hydrogen sulfide entirely in analysis, but the higher cost is discouraging. For confirmatory tests, however, only traces of dithiol are required so that the cost is very low.

Dithiol complexes with metals are remarkable in that all the colors of the spectrum are represented, with almost no two colors identical. Even when colors are similar they are often formed under entirely different conditions (see Table 2) or have a totally dissimilar appearance (e.g., Bi and Sn). Moreover, the reactions are highly sensitive and compare very favorably with established procedures. Frequently, the reactions are greatly superior, as in the cases of tin, cobalt, tungsten, and molybdenum.

Dithiol has a remarkable and analytically useful property not shared by hydrogen sulfide. To illustrate, let us imagine that hydrogen sulfide is passed into a hot weakly acid solution of copper and cadmium ions. Black cupric sulfide precipitates first, then quite suddenly the newly-formed precipitate becomes yellow as cadmium sulfide forms. Thus, a sharp change in color makes it possible to separate the two metals.

Such separations are rarely possible, however, because sulfides coagulate poorly and their colors show so little variation. Moreover, the colors of certain sulfides vary considerably with time immediately after they have been formed. With dithiol these difficulties do not arise for, added to a mixture of cations in solution, good separations usually result. Even in solutions containing many cations the color of the freshly-formed precipitate shows which element is being precipitated. It is often helpful to add a few drops of dense solvent (e.g., ethylene dichloride) to remove the precipitates as they are formed from the warm solution. In this way a change in color of the freshly-formed precipitate may be rendered at once more obvious. For example, by mixing 0.01 *M* solutions of cations, two at a time, and adding dithiol, the student can arrange the complexes in the order of their solubility products and at the same time he becomes familiar with their colors.

The mercaptide complexes usually precipitate with extraordinary ease, probably due to the presence of the hydrophobic aromatic ring. As the mercaptides are very insoluble dithiol can replace hydrogen sulfide on the surface of sulfide precipitates. Thus, if a colloidal solution or suspension of sulfides stubbornly refuses to precipitate, it may be boiled with a trace of dithiol. The colloidal sulfide particles become less easily wetted by water (i.e., become hydrophobic), coagulate rapidly, and precipitate. It follows, therefore, that in acid solution the value of hydrogen sulfide as a reagent for precipitating thiophilic cations is greatly enhanced by the addition of a trace of dithiol.

Diacetyldithiol (DADT) is an even better catalyst for improving precipitation by hydrogen sulfide. In acid solution this compound is stable and, unlike dithiol, is not volatile with steam. In dilute mineral acids, diacetyldithiol causes arsenates and molybdates to decompose smoothly within a few minutes, none of the usual difficulties being encountered. With the more common elements the precipitates obtained are the usual sulfides, since only a trace of the organic compound is added.

Table 2. Colors of Dithiol–Cation Precipitates

Formed in	Colorless	Brown	Black	Red	Orange	Yellow	Green	Blue	Purple or violet
10 *N* HCl	—	—	—	Pd Au (brown-red)	—	Te Se Rh (brown-yellow)	Re	W	Te (excess DT)
6-10 *N* HCl	Ge	Ru	Ir	—	—	Hg As(very pale)	—	—	Os
1-6 *N* HCl	—	—	Cu Co	Bi Sn(II)	Sb(III)	Ag	W Mo	—	Pt
1 *N* HCl or acetic acid	Cd Zn Ga In	—	Co Fe Ni	—	Tl	Pb Sn(IV)	—	—	—
Alkali including pyridine (Py)	Most cations	Mn	—	Fe(II) Sb(V)	Cu(NaOH) Tl	—	Ru(III) Cu(Py) Ni V	Co	—

Diacetyldithiol also coagulates the colloidal solution of sulfur obtained by acidifying a solution of thiosulfate.

In Group IV it is customary to dissolve the nickel and/or cobalt sulfide precipitate in aqua regia, or similar solvent, before testing for nickel and cobalt, respectively. This is unnecessary, however, because the precipitates immediately dissolve in a suitable DT or QDT solution to give colors characteristic of the two metals.

Like hydrogen sulfide, dithiol is difficult to keep in the free state. In solution the disulfide precipitates, just as in a solution of hydrogen sulfide free sulfur is precipitated. Dithiol is most conveniently stored as the colorless zinc complex (ZDT), $C_7H_6S_2Zn$, which can be kept indefinitely. It is usually sufficient to add this *directly* to the solution to be analyzed. The reactions of DT are immediately obtained on warming. In very rare instances zinc must be absent, and when this is so ZDT is added to hot dilute acid and the DT is extracted with chloroform or ethylene dichloride. Alternatively, a solution of DT can be obtained within a few seconds by warming DADT with pyridine or alcholic KOH.

It is hoped that this brief summary of the uses of dithiol and catechol-like reagents may point the way to a more rational approach to inorganic analysis. Although DT is somewhat more expensive, on a weight basis, than many other reagents, the quantities required are small. For example, a class of 15 students, which employed ZDT for confirmatory tests only, used less than 0.5 g in 30 hours of practical analytical work. Savings in servicing, by making one or two reagents do what many did before, are also considerable. Again, the time of the student (or research worker) is frequently wasted in looking for reagents so that a reduction in their number is to be welcomed.

Paradoxically enough, the older chemists were probably correct in believing that qualitative inorganic analysis requires but few reagents. Perhaps the modern trend to discover one reagent specific for each cation is a retrogression!

The reagents and experimental procedures employed in the qualitative analysis of cations are given in the following section. Readers requiring further information are referred to the recent papers by Clark.[2] The use of ZDT as a reagent for ketose sugars is described by Clark and Neville.[3]

Reagents

Zinc Dithiol (*ZDT*) is a stable white powder affording a convenient source of dithiol (DT). It may be used dry or 0.5–1.0 g may be rubbed with alcohol and made up to give a suspension in 100 ml of 95% alcohol. The bottle is labeled "shake before use" and is provided with a teat-dropper. Between 1–4 drops suffice for most tests.

Procedures

(1) Add ZDT directly to the solution to be tested. Only rarely (as in testing for Zn and Mn) does the zinc interfere.

(2) Add ZDT to alcohol. Add a few drops of conc. HCl. A colorless clear (or nearly clear) solution of DT is obtained. The solution should be used within 2–3 hours.

(3) If DT free from Zn is required, shake dry ZDT with dil. HCl and heat until oily drops of DT appear. Add a dense solvent (chloroform or ethylene dichloride) and cool. Remove portions of the lower layer, which is a Zn-free solution of DT, with the aid of a dropper as required. If the lower layer is not clear, insert a plug of cotton before using the dropper.

Diacetyldithiol (*DADT*) is a white crystalline solid, mp 48°, soluble in all organic solvents. Should be stored in a dark bottle. A metal spatula should not be used in handling, as discoloration may result.

Procedures

(1) To prepare a coagulant for sulfides and sulfur, dissolve approximately 1 mg in 0.5 ml of alcohol. Use one drop. The solution is not stable beyond a few weeks.

(2) Melt one pellet of KOH (0.1 g) with one drop of water. Add 1 ml of alcohol and a few crystals of diacetyldithiol. Heat and hold at the boiling point for 10–15 seconds. The solution now contains DT free from Zn.

(3) Add a few crystals to 1 ml of pyridine. After warming, this mixture gives the reactions of free DT.

Quinoxaline-2,3-Dithiol (*QDT*) is a dark yellow stable powder, mp 345°, with decomposition.

Procedure

Dissolve 0.1 g in 50 ml 2*N* NaOH and add 1–2 g of sodium sulfide crystals. The solution is stable for 1–2 months, after which it reacts slowly and, eventually, hardly at all. Used as a test for Ni.

Uses of Reagents in Elementary Analysis

For the most part the tests are highly sensitive, and it is usually sufficient to employ one drop of the diluted test solution. Methods may be used on the traditional scale or, with obvious modifications (e.g., for "filter," read "centrifuge," etc.), for semimicro work. Owing to the violent gas evolution, however, the suggested separation for Group IIB is less suitable for the latter.

Preliminary Tests. As the consumption of ZDT is likely to be greater if the solid is used, these tests may be omitted with elementary students if desired.

I. To a drop of the test solution add excess conc. HCl:

(1) Add solid ZDT in excess and warm.

(2) Then add slowly 3–4 vols. of water, noting any colored precipitates formed. Boil.

(3) Finally, add sodium acetate crystals in excess.

(1) White milky suspension in strong acid probably indicates As. Oxidizing agents act similarly. If the test is repeated with the addition of a reducing agent, e.g., crystals of $SnCl_2$, the reaction is highly selective. Some rarer elements give colored precipitates which coagulate rapidly and do not usually interfere.

(2) Very pale yellow ppt. Characteristic appearance:

Climbs wall of tube	Hg
Yellow precipitate	Ag
Black or gray precipitate	Cu
Orange precipitate (oily on boiling)	Sb
Magenta-red precipitate	Sn
Brick-red precipitate	Bi

Since the precipitates form at different acidities and coagulate rapidly, it is frequently possible to identify the presence of more than one metal. However, owing to the oily nature of the product that it gives, Sb tends to mask other reactions.

(3) Bright yellow precipitate ..... Pb
Black or dark precipitate ..... Fe, Co, Ni

(With Fe, Co, Ni, excess DT colors the liquid. See below.)

II. To a drop of the test solution add a few drops of pyridine and 0.1–0.5 mg of ZDT (or a few crystals of DADT). Warm:

[2] Clark, R. E. D., *Analyst*, **82**, 177, 182, 760 (1957); **83**, 103, 396, 431 (1958); **84**, 16 (1959).

[3] Clark, R. E. D., and Neville, R. G., *J. Org. Chem.*, **24**, 110 (1959).

Green color ..... Cu
(Possible confusion with Ni)
Blue color ..... Co
Magenta-red color (intense with DADT) . Fe

The original substance with NaOH and excess ZDT gives an *orange* color if Cu is present.

Precipitation of Group 2 Metals by Hydrogen Sulfide. Adjust the acidity of the solution to 0.3–0.4 *N* in the usual manner. Add one drop of DADT in alcohol (see above). Pass H_2S as usual. Finally add a further drop of reagent and boil off the alcohol. Proceed as usual.

Confirmatory Tests for Cations

Group I. Separate as usual.

Hg. Dissolve black residue on filter in HCl + Br_2-water (a trace of potassium chlorate may always be used in place of Br_2-water). Boil off Br_2 and dilute. Add ZDT. Pale yellow precipitate tending to creep up walls of tube indicates *Hg*.

Ag. To a few drops of ammoniacal solution add large excess conc. HCl and warm until first formed precipitate redissolves. Add ZDT. Add drops of water slowly. Yellow ppt. forming suddenly indicates *Ag*.

Pb. To solution containing $PbCl_2$ in *hot* water add ZDT. Brilliant yellow ppt. indicates *Pb*.

Group II. Precipitate Group II metals as above using H_2S and DADT. Separate Group IIA from Group IIB as usual, using 0.5–2.0 *N* KOH or 1% LiOH.

Group IIA. Separate in the usual way. (Good separation can be effected by means of DT but the method is likely to prove expensive for elementary classes.)

Hg. Dissolve and test as in Group I.

Pb. Precipitate consists of $PbSO_4$. Dissolve a few mg of ZDT in dil. NaOH and pour solution through the filter. The $PbSO_4$ is immediately stained a brilliant yellow. Incomplete removal of Pb from the solution by means of sulfuric acid does not interfere with subsequent tests.

Bi. Pour hot dil. HCl through the filter to dissolve ppt. of $Bi(OH)_3$. To portion of filtrate add ZDT and boil. Chill quickly. Brick-red ppt., partly or wholly soluble on boiling, indicates *Bi*.

Cu. To 1–3 drops of ammoniacal solution add excess ZDT. Intense orange color indicates *Cu*. (If ZDT is not in excess a dark ppt. forms.)

Cd. To second portion of ammoniacal solution add excess $Na_2S_2O_4$ and boil. Filter from Cu. Pass H_2S. Yellow ppt. indicates *Cd*.

Group IIB.

To the alkaline extract from Group 2A add an equal vol. of conc. HCl. Heat to boiling. Filter from As_2S_3. To the filtrate add half its vol. of ethylene dichloride followed by Zn dust until the violent reaction moderates. Sb as metal collects in the lower solvent layer and $SnCl_2$ remains in the dilute acid. (If the acidity has been lowered too much by the Zn, Sn may precipitate as metal together with Sb. It is readily dissolved by the addition of more acid in which Sb is insoluble.) Use dropper to separate layers.

As. Dissolve ppt. in conc. HCl + Br_2-water. To 1 drop add conc. HCl in excess plus crystals of pure $SnCl_2$ or NaH_2PO_2. Add ZDT and warm. Immediate white emulsion (turning red with much As present) indicates *As*.

Sb. To the suspension of metal in ethylene dichloride add conc. HCl and Br_2-water and heat. Boil off Br_2 and solvent. Add ZDT and dilute somewhat. Heat. Orange ppt. melting to orange drops on surface indicates *Sb*. (*Note:* Sb(V) gives a magenta-red color with Zn-free DT and pyridine. This reaction is much more sensitive than the above, but confusion with the similar color given by Fe is possible.)

Sn. To aqueous layer containing $SnCl_2$ add ZDT and warm. Magenta-red ppt. indicates *Sn*.

Group III. Separate as usual.

Fe. Transfer a trace of the ppt. of $Fe(OH)_3$ on the end of a glass rod to a few drops of pyridine containing either (*a*) a few crystals of catechol, or (*b*) a trace of DADT or Zn-free DT. (If ZDT is used the color is much less intense.) Warm. An intense blue or red color, respectively, indicates Fe.

Cr. Acidify a portion of the solution containing chromate with dil. H_2SO_4. Boil to destroy H_2O_2. Cool. Add a few mg of catechol. Solution darkens, finally becoming black if Cr is present. (The test has proved more reliable and more sensitive than the usual peroxide test, but fails if hydrogen peroxide has not been mostly destroyed.)

Al. Test with alizarin or other catechol-like reagent as usual.

Group IV. Separate as usual. After extracting with dil. HCl, test a portion of the black ppt. for Co and Ni directly.

Co. Transfer a trace of the ppt. on the end of a glass rod to a few drops of pyridine containing ZDT. Warm gently. Sky-blue color indicates *Co*. (Excess of Co or too little ZDT may give rise to a greenish color which is equally definite.)

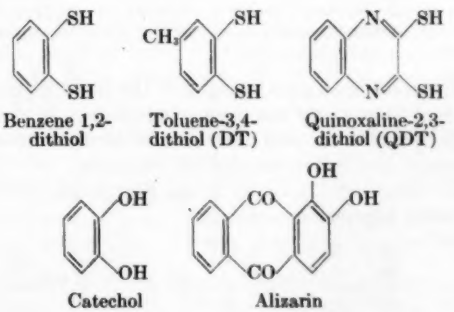
Ni. Transfer a trace of the ppt. to a few drops of QDT reagent (see above). Warm. A red or orange color indicates *Ni*.

Mn. Dissolve ppt. of MnO_2 in HCl by boiling. Add sodium acetate crystals in excess and Zn-free DT. Intense greenish brown color indicates *Mn*.

Zn. Present as sodium zincate in alkaline filtrate. Acidify with acetic acid. Add Zn-free DT in ethylene dichloride and shake. In presence of Zn a bulky white ppt. forms in the droplets of solvent which may appear to solidify.

[4] MORRISON, D. C., AND FURST, A., *J. Org. Chem.*, **21**, 470 (1956).

[5] SKOOG, D. A., LAI, MING-GON, AND FURST, A., *Anal. Chem.* **30**, 365 (1958).



The Cover

We gratefully acknowledge the permission of the Eli Lilly and Company to reproduce a portion of the photomicrograph that appeared in *Research Today*, **12**, No. 1, 5 (1956). It shows a subcutaneous fibrosarcoma induced in a rat by benzpyrene 1070X. Note the variation in cell size, especially in those undergoing mitosis.

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Common sources of confusion;

Electrode Sign Conventions

The subject of electrode sign conventions has received attention from many eminent chemists including Nernst, Gibbs, Lewis, and Latimer.[1] Some of the more recent remarks which have been made on the subject are included in references (*1–7*).

This subject has been worked very hard but some areas of misunderstanding still persist. It is hoped that a consideration from yet another viewpoint of two of the main sources of misunderstanding will be helpful.

One of the biggest single sources of confusion about the sign of electrode potentials stems from a failure to appreciate the simple but very important distinction between an actual physical electrode and the conceptual notion of a half-reaction. J. J. Lingane (*8*) first pointed out the importance of this distinction. In Lingane's words:

> ...The confusion arises from failure to recognize that "emf, of a half-reaction" and "potential of an actual electrode" are distinctly different concepts. The sign of the emf of the half-reaction at an electrode may either be the same or opposite to the sign of the potential of the actual electrode with respect to some other electrode.
>
> ...Although the sign of the emf or potential of a half-reaction depends on the direction in which the reaction is written the sign of the potential of the actual physical electrode at which the half-reaction occurs with respect to the sign of the potential of the other electrode is, of course, fixed or invariant. ...The potential of an actual electrode (observed physical quantity) is distinct from the thermodynamic concept of the potential or emf of a half-reaction (defined quantity).

This statement goes straight to the heart of much of the confusion about electrode potentials. It also does much to clarify the real difference between the so-called European and American sign conventions.

An author who adheres to the European convention will write expressions such as:

$$\left.\begin{array}{l} Zn = Zn^{++} + 2e^- \\ Zn^{++} + 2e^- = Zn \\ Zn/Zn^{++} \\ Zn^{++}/Zn \end{array}\right\} \qquad E^\circ = -0.76 \text{ volt}$$

That is, the standard potential of the zinc-zinc ion electrode is taken as −0.76 volt regardless of the way in which the couple is represented. This convention has to do with the potential of an *actual physical electrode* coupled with a standard hydrogen electrode in a cell. Since the potential of a standard zinc electrode is always −0.76 volt with respect to the standard hydrogen electrode regardless of the orientation of the cell on the laboratory bench, advocates of the European sign convention insist on always associating the number −0.76 with the zinc-zinc ion couple. The sign of an electrode potential is never varied in the European Convention.

What is commonly understood as the American sign convention (begun by Lewis and Randall and followed by Latimer) *does not* have to do with an actual physical electrode but rather with a half-cell reaction conceived on paper. American sign convention adherents write:

$$Zn = Zn^{++} + 2e^- \qquad E^\circ = +0.76 \text{ volt}$$

or equivalently,

$$2e^- + Zn^{++} = Zn \qquad E^\circ = -0.76 \text{ volt}$$

These two expressions mean that the spontaneous tendency is for zinc metal to be oxidized to zinc ion and two electrons, the standard free energy change being given by $\Delta F^\circ = -E^\circ n\mathfrak{F}$. With the American Convention the sign of the standard potential of a half-cell reaction is bivariant according to the direction in which the half-cell reaction is written on the paper.

Lewis and Randall and Latimer and their disciples have arbitrarily chosen to list their values of standard half-reaction emf's for half-reactions written as oxidations. Accordingly one most often sees expressions such as

$$Zn = Zn^{++} + 2e^- \qquad E^\circ = +0.76 \text{ volt}$$

The fact that the signs of these values for the standard emf's are just opposite to the signs of the standard electrode potentials according to the European Convention has led many authors to state that the European and American Conventions differ only in being opposite ways of measuring the same physical phenomenon. Kortüm and Bockris (*9*) and Delahay (*10*), for instance, explain that in the European Convention a potential difference is measured from electrode to solution while in the American Convention it is measured from solution to electrode. Strictly speaking this is not the case. The European Convention expresses explicitly the sign of a potential difference between actual physical electrodes but the American Convention does not. The standard half-reaction emf's given by Latimer (which are always cited as the chief example of the American Convention in action) give information on the tendency (or lack of it) for the given half-reaction to proceed as written; they are *not* simply European electrode potentials measured in the reverse direction (*11*).

Another major source of the confusion about signs of electrode potentials has been that in trying to maintain the fundamental distinction between the sign of a physical electrode and the sign of a standard half-reaction emf one is constantly using the words "positive" and "negative" in two very different senses.

Contribution No. 2384, Gates and Crellin Laboratories of Chemistry.

[1] A very complete bibliography is given in reference 2.

The difference between a *positive* and a *negative* free energy change (both of the same absolute magnitude) is thermodynamic, and not at all the same as the electrostatic difference between a *positive* and a *negative* potential difference between two electrodes (both potential differences being of the same absolute magnitude). The former positive-negative relation distinguishes between a tendency for a chemical system to change, or not to change, in a specified direction; the second positive-negative relation distinguishes between one kind of charge and its opposite.

The reason that the European electrode potential for, say, zinc, is −0.76 volt (i.e., 0.76 volt negative) is because *negatively* charged electrons are liberated at the zinc electrode. The completely separate reason that the American standard half-reaction emf for $Zn = Zn^{++} + 2e^-$ is $E^\circ = +0.76$ volt is because the thermodynamic tendency is for this reaction to proceed from left to right as written, i.e., for electrons to be liberated in the zinc electrode (thus making it negative with respect to the S.H.E.).

White and Black; Positive and Negative

It is only a (possibly unfortunate) coincidence that the same two words, "positive" and "negative," are used to describe both the two opposite senses of the free energy changes which accompany chemical changes and the two opposite kinds of electrical charge. The fact that the same word, "negative," is used to describe the sign of the charge on the electron and the sign of the free energy change which occurs when a system proceeds spontaneously towards equilibrium should not lead one to regard these two separate entities themselves as related. Even though the charge on the electron has been described as negative there is no reason to expect correspondence between a negatively charged electrode and a negative half-reaction emf. There is no relation whatsoever. The negativeness of an electron's charge (which is responsible for the negativeness of a physical electrode's potential) is simply not the same as the negativeness of a half-reaction emf—the two are incomparable.

If, in the interest of clarity, one were to insist on complete singularity of meaning for the words to be used in specifying pairs of opposites, then once the words "positive" and "negative" (or "plus" and "minus") were adopted to describe, say, free energy changes, it would be necessary to choose other words to describe other pairs of opposites which were not opposite in the same sense that a positive and a negative free energy change are opposite. For instance, one could distinguish between the charge on the electron and that on the proton by speaking of the electron's charge as *black* 1.603×10^{-19} coulombs and the proton's charge as *white* 1.603×10^{-19} coulombs, where the colors are used to indicate the oppositeness of the charges.

If Benjamin Franklin had decided to call the two opposite kinds of electric charge black and white instead of negative and positive he would very probably have saved electrochemists from much of their confusion over signs.

If the electron's charge were black the European Convention would not be that the standard electrode potential of zinc is −0.76 volt but *black* 0.76 volt. However, even if the electron's charge were black Lewis and Randall and Latimer would still write:

$$Zn = Zn^{++} + 2e^-; \quad E^\circ = +0.76 \text{ volt}$$

and

$$Zn^{++} + 2e^- = Zn; \quad E^\circ = -0.76 \text{ volt}$$

And now the temptation is gone to try to compare the sign of a physical electrode (given in the European Convention) and the sign of a half-reaction emf (given in the American Convention). One doesn't compare blackness with negativeness.

In the author's opinion the use of black and white to describe the opposite kinds of charges would contribute to a decrease in confusion. Because of the prejudices of tradition, however, the general adoption of such a practice does not seem a realistic possibility. One is therefore forced to live with free energy changes which are positive and negative as well as with positive and negative charges. The only way to avoid the latent confusion which results from using words with several meanings is to keep clearly in mind the physical realities which the words describe.

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Laboratory Notebook Survey

The experiences and opinions of 86 industrial research companies are included in a Laboratory Notebook Survey recently made by Cargill, Incorporated. The gist of the survey seems to be that there are still many problems connected with the proper choice and proper use of laboratory notebooks as a means for keeping research records, with special emphasis on the importance of careful, detailed records dated, signed, and witnessed for the best possible protection in case of patent litigation.

Copies of the complete survey results are available free from The Research Library; Cargill, Incorporated, 200 Grain Exchange; Minneapolis 15, Minn.

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Radiation Effects on Solids, Including Catalysts

The first clearly visible intimation of radioactivity was in certain minerals, where "pleochroic haloes" (*1*), minute, concentric shells of coloration, had been known (but not understood) for many years. And, of course, both radioactivity (*2*) and X-rays (*3*) were discovered through an effect upon a solid, the darkening of a photographic plate. Similar effects, both physical and chemical, were discovered as soon as appreciable amounts of radiation became available from radioactivity and from cathode ray tubes. During the ensuing 40 years, most of the chemical interest in radiation was directed at gases and liquids, because of the hoped-for simplicity of the former and the relevance of the latter to biological systems. Work with solids was confined largely to physical effects, such as coloration and luminescence.

All kinds of radiation research were greatly accelerated during and after the second world war. Nevertheless, about the same division of emphasis prevailed, with most of the work in chemistry continuing to be directed at liquids. This reflects partly a preoccupation with practical matters, radiobiology, and fluid fuels for reactors, and partly, probably, a prejudice for using fluid systems for basic studies in chemical reactions. The study of physical changes produced in solids experienced the same sharp increase as did that of chemical changes in liquids, for the practical reason that radiation damage to solid reactor materials (fuels, moderators, structural materials) needed to be measured and understood, and for the basic scientific reason that radiation damage was a new technique for the study of solids.

A large share of the information available about the effects of radiation upon solids, therefore, refers to physical rather than to chemical changes, and a considerable portion of this discussion will be concerned with material that is not ordinarily classed as radiation chemistry. It is hoped that this is not inappropriate, however, for it should give a more coherent picture of the whole range of solid effects and will provide a background for those completely unfamiliar with the field.

The last part of the paper is devoted to phenomena at the surfaces of irradiated solids. These are observed through chemical changes produced in or by a liquid or gaseous phase in contact with the solid, but in at least some of the cases the origin of the effect is in physical changes in the solid.

Primary Events

A complete understanding of the ultimate physical and chemical effects of high-energy radiation upon solids obviously requires a similar understanding of all of the events from the first interaction between the radiation and the solid to the final state of the altered system. However, the details of these interactions are complicated, neither experiment nor tractable theory is available at many points, and it is possible to give an elementary account of the ultimate phenomena with only a qualitative picture of the initial events.

The primary effects of the interaction of matter with high-energy radiation, either electromagnetic or particulate, are electronic excitation (including ionization) and displacement of atoms, the relative amounts depending upon the kind and energy of the radiation, and somewhat upon the nature of the sample of matter. Electromagnetic radiation (gamma rays and X-rays) and electrons produce primarily ionization (excitation short of ionization will be understood to be included), the bulk of it arising from the further cascades of ionization produced by the electrons first detached. To a crude first approximation, which nevertheless is sufficient for this discussion, the course of ionization in a solid will be little different from that in a gas, except for the roughly thousand-fold closer proximity of successive events in the solid because of the greater density of electrons in the condensed phase. The distribution of energy between excitation and ionization, and even the stopping power itself, are certain to be altered by the influence of the solid on the binding of the valence electrons, but any detailed calculations are beyond the range of present theory (*4*). It should be noted that direct experimental information about the amount and distribution of ionization is available only for gases (ion collection and cloud-chamber experiments), and that inferences about the situation in condensed phases have at present only qualitative significance.

A small amount of atomic displacement also can result from electron irradiation. Electrons at almost all velocities lose energy primarily by excitation of electrons in the matter traversed, the probability of an elastic collision with an atom as a whole being very small except at energies below a few volts. Furthermore, the small mass of the electron makes it impossible to transfer much momentum to a massive atom unless the electron has an energy of at least 0.5 Mev (for an atom of atomic weight between 50 and 100), when the laws of elastic collision allow transfer to the atom of the 25 ev

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[1] Operated by Union Carbide Corporation for the United States Atomic Energy Commission.

necessary on the average for displacement in a solid. Thus electrons energetically capable of displacing atoms are in a range of energy where the probability of that type of collision is very small. Nevertheless, fast electrons can produce enough displacements to be significant, and since such electrons can result from scattering of gamma (or X-) rays of high energy, displacements arise also from irradiation with them (*5*).

Other mechanisms of low probability have been suggested for the production of displacements by conversion of ionization and excitation energy (*6–8*).

Massive charged particles also lose energy through ionization and excitation (above energies where the velocity of the particle is comparable to electronic orbital velocities) and by displacement. The transition to displacement with falling energy occurs, however, at a much higher energy than with electrons, and the masses are more favorable for momentum transfer, so that displacement is a much more important effect here. An idea of the magnitudes involved can be obtained from the table taken partly from the review of radiation displacements by Kinchin and Pease (*9*). It is clear from this that irradiation with massive particles is the more efficient way to produce atomic displacements for study, but also that one cannot completely neglect the displacements produced by those radiations usually used primarily to produce ionization.

Since an atom of a solid, set in motion by collision with an energetic particle is itself capable of ionization and displacement, one must consider the secondary effects so produced. Since the distances between collisions are rather small for the energies usually thus imparted to an atom, the energy which it possesses will be dissipated in a relatively small volume of the solid. Instead of trying to account for all these events on the atomic scale, one may adopt the simplifying hypothesis of the "thermal spike," and attribute the changes in the solid to brief, intense heating of minute volumes. Thus, an atom projected with 300 ev (not unusual in bombardment with Mev deuterons) has a range of about 30 Å in copper. That energy dissipated in a sphere 30 Å in diameter (containing 1100 atoms) would raise the material to the melting point (1083°C) in some 5×10^{-12} seconds, assuming that the macroscopic thermal conductivity can be used. The local high temperature would of course decay rapidly, and after 20×10^{-12} second a zone only 60 Å in diameter would have an average temperature of only 150°C.

It is not yet certain where or whether such spikes really do contribute radiation damage essentially different from that expected from the individual-displaced-atom picture (*10, 11*). It is, of course, naive to apply macroscopic reasoning about thermal conductivity to events within a few atom-distances and lasting over times of only 10 to 100 atomic vibrations. Nevertheless, the thermal spike is a conceptually simple approach to part of the radiation damage process in solids. It is related closely to the "point-heat" concept of radiation damage to living material suggested in 1923 by Dessauer (*12*).

A final effect of radiation that need only be mentioned is that of transmutation. This is a rather improbable process in most materials, even with thermal neutrons, and unless the product atom has very special properties for the phenomenon under study, the effect will hardly be noticed. The table contains entries comparing this effect with the displacement process for three elements of different neutron capture cross section.

Types of Solids and Imperfections

To follow the consequences of the primary radiation-produced events just described, it is necessary to consider a little more about solids than their mere rigidity. A starting point is the ideal crystal, consisting of atoms, molecules or ions of the substance concerned located on the points of a space lattice, and restrained there elastically by interatomic forces of attraction and repulsion. This is sufficient to explain the symmetry in shape and in other properties of crystalline solids. Such solids fall into four main classes, which may be regarded as representing a progression of greater localization of electrons. A metal is a regular arrangement of positive ions in a sea of electrons belonging to the whole crystal. A valence crystal (diamond) is a regular arrangement of atoms joined endlessly in three dimensions by covalent bonds. A molecular crystal is an array of molecules, held together by van der Waals' forces (naphthalene) or hydrogen bonds (ice), because neither charge nor ordinary covalent bonds are left over to join the individual units strongly to each other. An ionic crystal (NaCl), the ultimate in electron localization, is an array of positive and negative ions bound by electrostatic forces. A type intermediate between metals and covalent crystals, the semiconductors, represents a compromise between them in electron-localization. At low temperatures few electrons belong to the crystal as a whole, but the number increases as the temperature is raised. Germanium and graphite are examples. Some ionic crystals are semiconductors (ZnO) but it is thought that this is not a property of a perfect crystal of this type.

If vibrations of the constituent particles of a perfect crystal are assumed, then many of the characteristic properties of these various solid types can be understood, including thermal expansion, compressibility, heat capacity, electronic conduction in metals, and others. However, many properties cannot. For instance, a perfect crystal of aluminum should behave elastically up to shear stresses around 4×10^{10} dyne/cm², on the basis that the shear stress at the elastic limit should be around $^1/_6$ of the shear modulus if adjacent perfect planes of atoms move parallel to each other (*13, 14*). The observed elastic limit is only about 4×10^6. Many other properties, diffusion, color, luminescence, and others, are likewise not understandable on the assumption of perfect crystals.

Since about 1926, those properties of crystalline solids not understandable in a perfect solid have begun to be explained by the assumption of certain kinds of imperfections, some of which have proved to be important in radiation effects, as well as in other phenomena (*15*). These imperfections are of two classes, point defects and dislocations.

Point defects are the simpler to describe. They are either misplaced elements of the perfect crystal or atoms of an impurity. A *vacancy* is a lattice site from which the normal occupant (atom, ion, molecule) is absent. It is often called a Schottky defect. An *interstitial* atom (or ion) is an atom in a position not occupied by one in the perfect lattice. The occupant may

be a normal constituent of the lattice or an impurity. If a normal constituent of the lattice is removed to form a vacancy and placed itself interstitially, the pair of misplaced atoms is called a Frenkel defect. If it is removed to the surface and there occupies a normal lattice position (as part of a new atom layer) only the vacancy (a Schottky defect) exerts any unusual properties.

Instead of occupying an interstitial site, an impurity may substitute in a normal lattice site, but its different chemical nature will give rise to special effects even in a normal position.

The electron distribution in a perfect crystal is as regular as that of the atoms, although it differs in degree of localization from type to type of solid. The point imperfections just described may, however, distort the electron distribution. An electron may be "trapped" at a point of unusual positive charge (at a negative ion vacancy). It will generally be necessary to use energetic means to move the electron to this special site in the first place, either radiation or chemical energy. If an electron is removed from some part of a crystal (as by radiation) and trapped at some other point, the place from which it came will have an excess positive charge. The absence of the electron will also give mobility to the remaining electrons, a situation which can be described as the motion of the positive hole. This may itself be trapped by some local region of excessive negative charge.

The second type of imperfection is the dislocation (*16*, *17*), consisting not of one or two atoms completely out of position, but of many planes of atoms displaced somewhat and to different degrees from their ideal positions. Such distortions express themselves on the atomic scale in mismatching of neighboring planes of atoms over a region of many atoms, the mismatch reaching a maximum at some line in the plane. This line is called the dislocation, an "edge dislocation" if the distortion can be thought of as a compression of one part of the crystal with respect to another, and a "screw dislocation" if it can be thought to result from a rotary shearing. In the latter, the adjacent rows of atoms near the dislocation line are mismatched by not being parallel, and are curved to follow the shear; in the former, they are parallel to each other and straight, but not properly opposed.

Edge dislocations facilitate slip under stress in the planes in which they lie, and are thought to be responsible for the plasticity of real crystals. The slip under shear of two portions of a crystal relative to each other along a plane containing an edge dislocation can also be described as the motion of the dislocation across the plane, like a wrinkle worked across a rug. Screw dislocations are believed to be important in crystal growth, because the tapering step which characterizes such a dislocation at the surface of a crystal furnishes a suitable nucleus for further growth.

Dislocations exist in all real crystals, arising during their original growth and being generated by any subsequent deformation. The density (number of lines intersecting a square centimeter) varies from 10^2 to 10^3 per cm^2 in the most nearly perfect crystals (carefully grown Si and Ge) to 10^{11} to 10^{12} per cm^2 in heavily deformed metals.

Both edge and screw dislocations have the property of binding point defects to themselves because of local strain, which makes them important during irradiation, when displaced atoms, vacancies, electrons, positive holes, and electronic excitation are moving through the material. These may come to rest at dislocations because of the local strain, and complementary defects (e.g., hole and electron) may recombine at a dislocation with transformation of the recombination energy into some other point defect. Dislocations in some transparent crystals can be "decorated" and thus made visible by causing a metal, e.g., sodium to diffuse into the crystal and to concentrate along the dislocations.

These point imperfections (impurities, vacancies, interstitials, trapped electrons, positive holes) and dislocations are important in understanding radiation effects in solids, partly because some are among the products of radiation, and partly because those already present affect markedly the course of events during and after irradiation.

Bulk Effects of Radiation

The final products of the excitations and displacements caused so generally by high-energy radiation are markedly affected by the medium in which they are produced, and it is therefore convenient to describe the secondary processes in solids according to solid type. This arrangement puts physical and chemical effects largely in separate sections, although, of course, the boundary is not sharp. Phase changes, which might be included in either, are put in a third section by themselves. A general review of all types of effect has appeared (*18*), as well as one devoted primarily to chemical changes (*19*).

Physical Effects

To begin by considering metals is perhaps sensible since they fall at one extreme in behavior, and because the lack of chemical effects lends simplicity. The ionization which is produced by radiation in a metal (unless it leads by recoil to a displacement) is without effect. No chemical decomposition can occur through ionization, and no persistence of ionization by trapping is possible. A positive hole resulting from ionization is rapidly refilled with an electron, because there are always electrons available in the sea of common electrons (the conduction band).

On the other hand, atoms displaced by massive bombarding particles (e.g., protons) or by recoil electrons can persist. An atom at an interstitial position is, to be sure, not stable with respect to the lattice vacancy from which it came (or to another), but if the vacancy is several atom distances away, the interstitial is metastable, being unable to return rapidly at temperatures where diffusion is negligible.

A single crystal of copper is soft, and gives only a dull thud on being struck with a mallet. A 15-minute irradiation in a reactor of modest flux (10^{12} neutrons/cm^2, sec) converts it to a tuning fork (*20*), and a week's irradiation raises the critical shear stress by perhaps a factor of 10 (*21*). The softness and deadness of the original material are attributed to a relatively high concentration of dislocations which are rather free to move, allowing plastic flow at a low stress and absorbing energy of vibration when the crystal is struck. The

marked effect of even a short irradiation is thought to be the result of "pinning" of these dislocations by the interstitials and vacancies. These are thought to migrate at room temperature to dislocations, where they remain because of the local stress. There they impede the oscillations of the dislocation, preventing absorption of energy and slip. Since dislocations are long, and can be pinned at any point along their length, this provides the necessary multiplication of the effect of a few point defects.

Electrical resistivity is an important property of metals and can be measured relatively easily during irradiation. Bombardment of copper at 12°K with 12 Mev deuterons leads to an easily measurable increase in resistivity, around a factor of 2 per 10^{17} deuterons/cm^2 (*22*). The increase is attributed to scattering of the conducting electrons by the vacancies and interstitials, which act like impurities or like thermal motion to destroy the perfection of the lattice which is required for low resistivity. Since this effect per interstitial and per vacancy can be estimated theoretically, the increase in electrical resistivity has been used to estimate the number of defects produced by a given bombardment.

It is satisfying that the simple picture given for radiation damage in metals is reasonably successful, but it should be pointed out that complications exist, for instance in the annealing of damage. About 35% of the excess resistivity from low-temperature neutron bombardment anneals out around 30 to 50°K, surprising at first sight, but understandable if close vacancy-interstitial pairs are involved. Some of the resistivity increase persists to well above room temperature, and the enhanced critical shear stress anneals largely between 575 and 700°K (*23*, *24*). The different temperature ranges of annealing are thought to correspond to different ways in which interstitials can migrate to vacancies at various distances. A simpler distribution is expected from electron bombardments, in which the displaced atom seldom has enough energy to cause further displacements, than from fast neutron or other massive particle bombardments. Estimates of damage from simple displacement theory, like those in the table usually are from 2 to 5 times larger than estimates based on physical properties measured after bombardment. These last are of course partly theoretical, since the change in property (e.g., resistivity) per displaced atom is known only from theory. It is believed that the "experimental" values are lower than estimates from displacement theory because of partial annealing during bombardment.

Radiation damage to semiconducting metals is even more marked than with typical metals. The principal permanent effects on the atomic scale are the production of Frenkel pairs, but the properties of the material are much more sensitive to such defects. Since only a very small concentration of electrons is available for conduction, the electrical properties will be very sensitive to any additional donors or acceptors of electrons, which interstitials and vacancies may be. One example only will be quoted to illustrate the sensitivity. Bombardment of *n*-type germanium with about 1×10^{15} deuterons (9.6 Mev) per cm^2 increases the resistivity by a factor of about 10^5 to 10^6, but further bombardment decreases it, somewhat more slowly. At the maximum of resistivity the germanium has become a *p*-type semiconductor (*25*). The effects are tremendously greater than with copper, where the change previously quoted for 10^{17} deuterons/cm^2 was a factor of only about 2.

Graphite, standing somewhere between the typical metallic semiconductors and valence crystals, is a complicated solid and will be mentioned here only because of its (recent) historical interest. As a moderator for neutrons in reactors, its properties under radiation have been of interest since Wigner suggested in 1942 the possibility of major radiation effects on dimensions, thermal conductivity, and stored energy, all important for reactor design and operation (*26*).

Valence crystals, such as diamond, are quite unlike metals in their manifestations of radiation damage, although the similar very stable and symmetrical bonding makes them alike in showing no quasi-chemical changes such as depolymerization or reaction of the matrix with displaced entities. Lacking conduction electrons, they can retain electronic dislocations as well as displaced atoms, and since they are generally transparent, these changes give rise to coloration and luminescence.

Diamond, the archetype of valence crystals, is remarkably resistant to visible effects of simple ionization, but acquires a most attractive (and, if thought natural, most valuable) green color on heavy-particle bombardment. This distinction was first clearly established by Lind in 1923 (*27*), using radon and radium salts. Later work with neutrons, electrons, and deutrons has revealed more details of the traps produced by displacement, using absorption spectroscopy (*28*) and paramagnetic resonance (*29*). The lack of widespread interest in valence crystals, in spite of their relative simplicity and adaptability to optical measurements, probably arises largely from the scarcity of different substances of this type, with a corresponding lack of opportunity to compare similar phenomena over a wide range of small variations.

This lack of richness of material is not felt with ionic

Displacements by Various Radiations

Radiation	Energy, Mev	Flux cm^{-2} sec^{-1}	Time	No. of displacements per atom in copper		
Neutrons	2	10^{13}	1 mo	10^{-1}		
Deuterons	10	6×10^{12}	10 hr	10^{-2}		
Electrons	2	6×10^{14}	10 hr	10^{-3}		
γ-rays	1.3	10^{11}	1 mo	10^{-8}		
				No. of transmutations per atom (cross section in barns[a] below symbol)		
				Al	Cu	Au
				0.2	4	96
Neutrons	Thermal	10^{13}	1 mo	5×10^{-6}	1×10^{-4}	3×10^{-3}

[a] 1 barn = 10^{-24} cm^2.

crystals, which exist in great variety. The typical ionic crystals, such as NaCl, represent the ultimate in electron localization. As in valence crystals, but not in metals, the lack of communal electrons yields transparency, and much of their interest as experimental material stems from this. Unlike both of those two classes, however, ionic crystals can transport electricity by ion movement, and study of this has led to important advances in understanding (*30*). Here, for the first time in the order of consideration selected, appears a hint of chemical change produced by radiation. This might appear with valence crystals, since it is a manifestation of trapped electrons, but it depends upon their reactions with other components of the crystal or with a solvent, the first of which does not lead to an easily detectable chemical species in diamond, for example, and the second of which is impossible because of the excessive stability of the matrix in the same example.

In the ionic crystals, effects of simple ionization are easily observed. Alkali halide crystals are colored even by X-rays and cathode rays, an effect that has been known since at least 1901 (*31*). The colors introduced in this way have played a central part in the development of present understanding both of the effects of radiation upon them, and of the properties of the original crystals themselves. The most thorough review of the subject is indeed entitled "Color Centers in Alkali Halide Crystals" (*30*), and the defects responsible for the most striking colors have long been known as "*F*-centers" (from the German "Farbzentren").

It is presently believed (*32*) that all alkali halide crystals contain appreciable concentrations of Schottky defects, both positive and negative ion vacancies in equal numbers, which, near the melting point, are in thermal equilibrium with the rest of the lattice (*33*). Although energy is required to form them, vacancies increase the entropy of a crystal containing them, and the free energy is therefore a minimum at some concentration greater than zero. The equilibrium concentration varies from about 10^6 per cm^3 at room temperature to about 10^{18} near the melting point.

The accepted picture of the colors introduced by radiation into the alkali halides is that suggested by de Boer in 1937 (*34*), in which an electron is trapped in a negative ion vacancy. The color observed is then the absorption of this one-electron quasi-atom (hole plus electron), and most of the other properties of the colored crystals (photoconductivity, photobleaching, paramagnetism) can be similarly rather well explained.

The *F*-centers can be produced by other means as well. The first observations were made on crystals colored by heating in the vapor of an alkali metal (*35*, *36*). The alkali atom is thought to lose an electron to the lattice upon being adsorbed. Since it is unaccompanied by a negative ion, there will be the equivalent of a vacancy, which may diffuse into the interior. The electron will be available to be trapped at a convenient halogen ion vacancy.

A complication in the simple picture of trapping at pre-existing vacancies is that a greater density of *F*-centers (up to 10^{19} per cm^3) can be produced by radiation than that of vacancies in the original crystal. It is evident that X-rays are able to produce vacancies in these materials, even though they do not transfer enough momentum directly to bring this about. One suggestion (*37*) is that dislocations serve as sites at which excitation energy from a primary event is expended locally by conversion into lattice vibration sufficient to displace one of the ions.

Production of new chemical species by irradiation followed by further treatment can be observed in the alkali halides. A water solution of X-ray irradiated NaCl is slightly alkaline and oxidizing (*38*), presumably because of the reaction of trapped electrons and holes on solution:

$$e^- + H_2O \rightarrow {}^1/_2H_2 + OH^-$$

and

$$\text{hole}^+ + Cl^- \rightarrow {}^1/_2Cl_2$$

About 1 chlorine atom and 0.1 OH^- ion were found for each vacancy estimated by density measurement of the crystal to have been produced by the irradiation. If the irradiated crystal was bleached by heating before dissolving, none of either substance was found.

Production of colloidal aggregates of alkali metal has been observed in crystals colored by vapor treatment. Illumination bleaches the color of the *F*-centers, and if this is done above room temperature it results ultimately in coagulation. It is not clear that this is impossible with radiation-colored crystals, but it seems not to have been observed.

In another class of ionic crystals, the oxides, little decomposition (no more than 10 atoms per 400 electrons of 1000-volt energy) was found from CeO_2, ThO_2, or ZrO_2, although it was pointed out that a back reaction might conceal a somewhat higher intrinsic radiation decomposition rate (*39*).

Chemical Effects

There are now left for discussion those solids, at the opposite extreme from metals, which are susceptible to radiation decomposition. A trace of this behavior has already been noted in the alkali halides, where trapped electrons and holes produce typical chemical changes, but in most cases only when solution of the crystal allows a reaction to occur. In solids which contain some covalent bonds (whether in ionic or in molecular crystals) the covalent bonds can be broken by excitation and ionization of the solid, and, characteristically, the reaction proceeds to formation of ultimate products in the crystal.

Such behavior is shown for instance by nitrates, chlorates, perchlorates, and bromates, but only to a slight extent by sulfates. The decomposition of alkali nitrates, first studied by Sterba in 1907 with cathode rays (*40*), typifies this kind of behavior. Nitrite ion and oxygen gas are observed in a ratio of about two to one upon dissolution in water or upon melting. That most of the final products are formed in the crystal is demonstrated first by magnetic-susceptibility measurements (*41*) which conform closely to the calculated value for the known amount of oxygen, if the oxygen is present as gaseous O_2 molecules. The other decomposition product, NO_2^-, has been identified in the intact, irradiated crystal through the absorption band at 3450 Å (*42*). The yields of nitrite from different irradiated nitrates range from less than 0.01 to 3 molecules NO_2^- per 100 ev. It is not certain whether a back reaction occurs. The yields per 100 ev in some

nitrates seem to decrease at high doses (around 10^{22} ev/g) (*41*), but not in KNO_3 (*43*) nor at low doses (5×10^{20} ev/g) in several other nitrates (*44*).

In the magnitudes of the yields and in the completion of the reaction *in situ*, the nitrates act much as do liquids, rather than as pure ionic crystals or valence crystals. Their behavior is dominated by the covalently bonded anion, and only somewhat modified by the fact that the anion is bound in a solid lattice.

Just how much the solid lattice affects the detailed results is of course the principal question of interest and should be discoverable through experiments with different nitrates. One general line of explanation that has been proposed (*41*) is that the "free volume" available to the excited anion determines the extent of recombination and hence the yield. The free volume appears to give a better correlation of yields than, for example, cation size, lattice energy, or any other simple parameter (*43*).

The ionic lattice in nitrates is not, of course, completely lacking in its own characteristic behavior under radiation. The spectroscopic results (*42*) indicate the presence of species which are probably similar to *F*-centers, although their behavior with dose and other features is more complicated because they can react with some of the chemical decomposition products.

A point of general interest in solid-state radiation decomposition is the mobility of the products. It is clear that the rigidity of the solid will, to a degree, restrict this, and it is important to obtain quantitative information about various species (particularly reactive intermediates) in various types of solid. In the case of the nitrates, the accumulation of molecular oxygen affords some such information. A measure of the mobility is given by the amount of oxygen in individual pockets if it is formed initially in a spatially uniform distribution. Such pockets must exist from the milky appearance of some irradiated crystals, and some rather inconclusive estimates of the oxygen content of the pockets (*41*) indicate a rather high mobility at room temperature. Heating leads to microscopically visible gas bubbles.

Solids with covalent bonds, susceptible to conventional radiation decomposition, also occur as molecular crystals, in which discrete molecules are bound in a lattice by van der Waals' forces or by hydrogen bonds. Organic compounds typify the first subtype, and because many compounds of interest happen to be solids, a number have been irradiated in the solid state. The behavior of many may be understood in outline (*45*) by considering the statistical redistribution of locally absorbed energy among the various bonds. For example, a long, straight-chain fatty acid has a larger proportion of C—H bonds relative to —COOH groups than a short member of the series, and would be expected to yield a higher ratio of H_2 to carboxyl decomposition products. Experimental values for the ratio $H_2/(CO + CO_2)$ are 0.5 for caprylic acid (C_7), 0.8 for lauric (C_{11}) and 1.2 for palmitic (C_{15}) (*46*). The absolute value of the yield from a single type of bond is expected to depend upon the strength of the bond involved as well as upon the frequency of its occurrence in the molecule under study.

These considerations apply as well to solids, liquids, or gases, and suggest no special solid state effects. This expectation is fulfilled in the gamma radiolysis of CCl_3Br (*47*), where no change in the rate of Br_2 production is noted either at the melting point (−5.6°C) or at a solid phase transition at −35.5°C. In other cases, large effects of state are observed, but these can sometimes be qualitatively explained (*45*) by the caging of freshly formed fragments by the surrounding molecules of the solid, a process obviously promoting recombination, and perhaps, with complicated molecules, leading to a radically different pattern of products. Whether a given deviation by a solid from behavior of the same compound as a liquid should be taken as evidence for special solid state effects beyond the greater cage-effect is difficult to say because of the complexity of organic molecules and the flexibility of theory. Some examples which suggest more subtle effects are given below.

There is direct evidence in the fluorescence of naphthacene-anthracene mixtures that energy from a primary absorption is transmitted through an organic solid over many atomic distances (*48*). Solid solutions with only 1 naphthacene per 10^4 anthracene show the green fluorescence of the naphthacene rather than the violet of the main constituent. If the material is dissolved in benzene, only the violet fluorescence of the anthracene appears. Similar conclusions about energy transfer from ionizing excitations (rather than optical, as above) can be drawn from studies of scintillation by solid solutions of phosphors like terphenyl in polystyrene (*49*). Although most striking for solids, similar transfer takes place in liquids also (*50*), as exemplified in liquid scintillation counters. Clearly, unusual efficiency or specificity in energy transfer must also influence chemical changes in solids where it occurs. The clearest evidence for this seems to be in high polymers (*51*), but, since that field is being discussed separately (*52*), it will not be treated here.

A purely chemical observation which points to unexpected complexities in the solid state is the enormous sensitivity to radiation of crystalline choline chloride $[(CH_3)_3NCH_2CH_2OH]Cl$. With gamma rays a G for decomposition of 354 was observed, compared to 92 for the bromide, a maximum of 29 for a series of other analogues, and less than 5 in aqueous or in alcoholic solution (*53*, *54*).

No mention has been made of another molecular crystal, ice, which is of particular interest because of the detailed information which is available for its liquid phase. Enough was said in a preceding paper (*55*) to indicate that this solid poses interesting problems; it will be passed over here with only a reference (*56*).

Examples have now been given of radiation decomposition in the principal types of solid in which it can occur. It is clear that a major cause of such distinctive behavior as appears is the rigidity of the solid state, restricting movement of ions, atoms, radicals and molecules. Here, and in a previous paper (*55*), have been described cases in which some direct evidence can be obtained about such restricted movement, about hydrogen atoms in frozen aqueous solutions and about oxygen molecules in nitrate crystals. It should be mentioned that scavenging techniques as well as conventional kinetic studies on accessible later products may give information about the mobility of the earliest chemical entities when those cannot be followed directly.

All solids have rigidity; crystalline solids have the further influential property of repetition of local environment. The degree of importance of this for decomposition is not clearly apparent, although it is determining in electronic conductivity and in the long-range transmissibility of excitation energy. The consequence of this property which is clearly apparent is that it makes possible the detailed investigation of the solid on an atomically local level by the various spectroscopic methods (*55*). This kind of investigation is obviously an important aid to detailed understanding of chemical effects.

In contrast to the previous sections on largely non-chemical effects, nothing has been remarked under decompositions on the influence of crystalline imperfections. These influences have not been ignored in recent research, but they do not appear to exert the almost universal and almost complete control here that they do over many physical properties. This is understandable, since even in a perfect region of a crystal ionization or excitation has a high probability of breaking a covalent bond. There are examples of major effects of degree of imperfection upon yield, for instance in C_2H_5I (*57*) and in frozen aqueous solutions (*55*), and the probable importance of defects under some conditions has been emphasized (*19*).

Phase Changes

Some solids, not susceptible to chemical decomposition, nevertheless may be made to undergo bulk changes by irradiation. Because the production of vacancies and interstitial atoms may increase diffusion rates, it is to be expected that solids in a metastable state with respect to another solid phase might transform under radiation. It is also possible that defects might nucleate and hence promote a similar transformation. Another possibility is the production of local temperatures (spikes) in the range of stability of a different phase, which might therefore grow in on a microscopic level.

Reactor irradiation at −196°C has been shown to accelerate the spontaneous transformation of white to grey tin on warming to about −20°C, where grey is the stable form (*58*). Precipitation (in alloys), ordering, and disordering are also observed to be affected by radiation in certain cases (*59*).

The "metamict state" of minerals has been known for many years, and represents a nearly complete disordering of a crystal by long-continued natural irradiation (*60, 61*). Such a crystal will usually exhibit the external form of a crystal but will appear amorphous to X-rays. Berzelius, in 1815, was apparently the first to note the striking release of energy on warming a metamict mineral, gadolinite (*61*).

Surface Effects of Radiation

Not all of the reaction possibilities involving radiation and solids have yet been touched on. Just as thermal or photochemical reactions in a gas or liquid may be modified by the presence of a solid (catalysis, photosensitization, wall effects), so may be the case in radiation chemistry. Likewise, radiation may affect the reaction of a liquid or gas upon a solid, as in corrosion. Finally, irradiation of a solid *in vacuo* may produce defects which will alter its subsequent reactivity when brought into contact with a medium which can react with it, or its catalytic activity toward a reaction catalyzed by the solid.

Radiation effects in colloidal systems have been observed and probably are, in some cases, manifestations of changes in the solid phase, or surface changes belonging to the present category of discussion. Because of their rather special interest, they will be dismissed with only some leading references (*62, 63, 64*).

Alteration by Solids of Radiolytic Reactions in Liquids

The presence of a solid with appreciable surface during the irradiation of a liquid or gaseous system might be anticipated to affect the results in a number of ways. Important influence of the solid can be imagined at three stages, as follows:

(1) During the excitation-ionization stage such energy may be transferred from the solid to adsorbed substrate molecules to give an increased yield, or, because of orientation on the surface, to give a specific sort of activation. Conversely, energy may be transferred in the other direction to give protection of adsorbed molecules.

(2) During the reactive-intermediate stage, a solid may act to increase the reaction rate of such intermediates formed in the adsorbed layer by simple increase of substrate concentration by adsorption. Reactive intermediates from the bulk substrate may diffuse to the surface, and there undergo catalyzed reactions. Reactive intermediates may, on the other hand, react with the surface and be protected from further reaction. Finally, the properties of the surface as a catalyst may be altered by adsorption of an active intermediate.

(3) Final product molecules may react catalytically on the surface to give new products.

Other modes of interaction may be imagined, but these will serve to illustrate the possibilities. Several of these seem to be represented in the small amount of published work in this field. It may be remarked that more information perhaps exists unpublished, since the possibility of industrial exploitation has been mentioned (*65, 66*).

Energy-transfer from solid to adsorbed molecules appears to be demonstrated by the work of Caffrey and Allen (*66*) on the radiolysis of pentane. Thus, a 10 wt % pentane–90% silica gel yielded hydrogen under gamma radiation at $G = 1.8$ for the energy absorbed in the mixture. Since bulk liquid pentane shows $G(H_2) = 4.2$ (*67*), the result expected in the mixture with no energy transfer is 0.4, less than one quarter of that observed. Because the effect on another kind of silica of known surface area showed a saturation at about the composition for a monolayer (4% pentane: 96% silica), it appears that the effect is limited to about one adsorbed layer, which is understandable if the transfer is, as appears, rather specific. The specificity is shown by the variation in H_2-yields from solid to solid, and particularly by the alteration in the relative yields of various hydrocarbons with different adsorbents, MgO, SiO_2, Fe_2O_2, Fe_3O_4 or $CaO{\cdot}2SiO_2$. While the enhanced total yields observed must represent an energy transfer at an early stage (ionization or excitation), the various highly specific results may arise there, or during the later reactions of free-radical intermediates.

Since photosensitization by ZnO is well known (destruction of paints containing ZnO pigment (*68*), photooxidation (*69*), production of H_2O_2 from H_2O (*70*)), it is not surprising that similar transformations should be observed with ionizing radiation. The production of H_2O_2 by gamma rays in NaOH solution is increased 4- or 5-fold by the presence of ZnO at 20 mg/cm³ (*71*). A smaller increase (15%) in radiation-reduction of Ce^{+4} in the presence of platinum was explained as simply an increased stopping power for the mixture, some of the extra gamma rays stopped in the heavy metal contributing electrons to the solution (*72*). Another example of energy transfer appears to be the radiation-oxidation of SO_2 in the presence of TiO_2 or of TiO_2-V_2O_5 catalysts (*73*).

Intervention of a surface at either of the first two stages has the possibility of protecting substrate molecules. In the X-ray inactivation of the enzyme deoxyribonuclease it was found that any one of several adsorbents added to an aqueous solution of the enzyme afforded considerable protection (*74*). The adsorbents, of different effectiveness, included cellulose, silica gel, bone ash and ion exchange resins. If adsorbent and solution were irradiated together, the enzyme actually adsorbed was strongly protected, but that in solution in contact with the adsorbent much less so. This argues against competitive protection against free radicals and for a specific protection in the adsorbed layer, but the complications of enzyme experiments are such that other explanations might suffice.

Modification of radiation-sensitivity of biochemical substances by addition of other substances having specific interactions with them (*75*, *76*) or by spreading in monomolecular layers (*77*, *78*) is also known, and although a solid phase is not involved, the effects of specific bonding or of orientation are suggestive of similar possibilities with solids. One may, of course, also attribute some of the variations in yields of different products in Caffrey and Allen's (*66*) results to preferential protection of certain bonds rather than to preferential enhancement.

Some experiments appearing to show effects of solids on secondary reactions of intermediates in aqueous solutions were described by Haissinsky (*79*). The examples are relatively complex (oxidation of KI and uranous sulfate, reduction of ferric-*o*-phenanthroline, decoloration of methylene blue), and, as the author remarked, more complete data are necessary for an interpretation.

Alteration of Surface Reactions by Simultaneous Irradiation

Radiation-corrosion is excessively complicated in the cases which have been of most interest, those of aqueous solutions of fissionable materials corroding stainless steel and zirconium alloys (*80*). It is clear that either radiation changes to the solid or radiation-formation of active species in the aqueous phase, or both, may be important. The more fundamental question of the effect of radiation upon electrochemical behavior at a surface has been studied (*81–83*). The available experiments can be interpreted in terms of the chemical substances produced by radiation in the liquid and their electrochemical reactions at the surface. This, of course, is determined by the nature of the electrode.

Influence of Prior Irradiation Upon Reactivity of Solids

Reactor-irradiated graphite has served to show the enhancement which stored energy can produce in a chemical reaction (*84*). This has been of practical interest because of the possibilities of graphite reacting with air in air-cooled reactors. At 300°C, graphite reacts slowly but measurably with pure O_2. While an unirradiated sample lost 0.06% in weight in 100 days, a similar sample irradiated to about 1×10^{20} *nvt* (n = neutron density, neutrons/cm³; v = average neutron velocity, cm/sec; t = time, seconds) lost 0.3%/100 days. Such a sample contains about 2.5% displaced atoms initially but probably only about 1% after heating to the reaction temperature. Since the increased rate persists even up to 25% oxidation (at a higher temperature, 400°C), it is not the displaced atoms only which are being more easily oxidized—they facilitate the oxidation of all or a large part of the sample.

Gamma rays present during oxidation increase the rate also, either by affecting the gas, or by energy transfer from the solid to the interface.

Influence of Prior Irradiation Upon Catalytic Activity

The connection between catalysis and radiation is rather old, and in a special sense even older. In the absence of clear ideas as to the nature of radioactivity, the chemical changes produced in the presence of radioactive material were sometimes referred to as "catalytic," a tribute to the mystery with which both phenomena were regarded. This point of view is not well documented (except in refutation) (*85*, *86*), but was current enough to be remarked upon by Lind (*87*).

During the period when radiation chemistry was being delineated and while, later, no more than two or three schools of research and a few isolated workers were exploring it, the subject of heterogeneous catalysis was growing feverishly. The development of the Ostwald ammonia oxidation process in 1902, and of the synthetic ammonia process by Haber in 1903–1907 were the beginning of a tremendous industrial growth. This was accompanied by a correspondingly large attention to fundamental studies, not only in universities but also in the large industrial laboratories, and by 1938 the outlines of a general understanding were discernible. Concepts that were part of this growing catalytic theory included: the recognition that catalysis was not explicable by a single, all-embracing principle; the importance of adsorption, including activated adsorption; the kinetics of heterogeneous reactions, particularly as influenced by adsorption; the specificity of certain catalysts for certain reactions; the apparent variability of different parts of the same surface as revealed by adsorption and by poisoning (hypothesis of "active centers"); criteria for expecting catalytic activity (paramagnetism, semiconduction); importance of lattice spacing; theory of absolute reaction rates.

Most of these concepts related to the reacting substance and not to the catalyst, or else treated the latter as a substance with certain *ad hoc* properties, which, however, were not related to detailed physical information about the solid. This was of course inevitable,

since the microscopic physics of real solids was only beginning to be developed during the previous two decades. One general point of view in catalysis (stemming from several of the aspects just cited) was, however, very apt for correlation with other properties of solids. This was the impression that catalysis perhaps was associated with only very special, and generally low concentration, features of or places on the catalytic surface. Some observations stood for uniformity, but there were many cases in which catalytic activity appeared to depend upon impurities or imperfections (not well defined) or special kinds of crystal site (edges, cracks, etc.).

By the end of another ten years, a period including unparalleled advances in use and understanding of solids, catalytic theory had absorbed enough of the growing theoretical basis of solid-state physics to produce fairly specific hypotheses relating catalytic activity of transition metals to the peculiarities of their electronic structure (holes in the *d*-bands, corresponding, in the solid, to the unfilled *d*-shells in the free atoms). Very briefly, such empty electronic levels can accept electrons of substrate molecules, binding the latter to the surface and altering their reactivity. Similarly, the properties of semiconductors to accept or donate electrons can be related to their ability to bind and alter reactivities of substrate molecules.

Such theories were largely tested by experiments on series of catalysts. For instance a series of alloys of nickel and copper can be made in which the *d*-band vacancies in the pure nickel are gradually filled as the concentration of copper increases and the effect of this progressive change on catalysis measured. Similar experiments can be done using doping of a semiconductor to change its type gradually from *n*- to *p*- or vice versa. Results of such experiments have been rather convincing, but the difficulty remains that not exclusively one property is changed by alloying. So is lattice spacing, for instance, which has been sometimes accorded great importance in catalytic theory (*88*).

Further, these hypotheses and these experiments have little specific to say about the problem of active centers, whether they have the widespread importance once attributed to them, or whether they exist at all, or are but artifacts introduced by the interaction between adsorbed molecules on a uniform surface.

The existence of hypothetical connections between catalysis and special sites on catalysts, the connections between paramagnetism and catalysis, the paramagnetism of *F*-centers and other defects, and the possibility of producing certain defects by radiation led in 1949 (*89*) to the initiation of experiments intended to see if any radiation effects on catalysts could be demonstrated, and if so, if they could be exploited in the service of catalytic theory.

Such experiments were thought to have two particularly interesting advantages. One is that they can be conducted on a single sample of a catalyst, with no complications from sample variability, and without the introduction of extraneous changes, as by alloying. The other is that the effects are largely local, and that some of the properties suggested as important in active centers (paramagnetism, local strain, abnormal atomic spacing) are present in the point defects.

As implied above, the early experiments on the irradiation of catalysts were done before theory was well enough developed to provide any useful guide. Both preirradiation to alter the catalytic activity in advance of testing, and simultaneous irradiation and activity testing were tried, and although the latter belongs really in a previous section it will be included here for convenience. Changes in activity were found with platinum as a catalyst for SO_2 oxidation (*90, 91*) (an increase) and for H_2O_2 decomposition (*92*) (a decrease), but in both cases the catalyst was irradiated in the presence of water, and the changes are attributed to radiolysis products adsorbed on the catalyst. Irradiation in dry air did not affect the activity of platinum for SO_2 oxidation (*91*). All of the early experiments known to the author are cited in reference 96.

Experiments undertaken more recently have given conclusive evidence of radiation effects on a variety of catalysts. This greater success undoubtedly stems partly from the more intense radiation sources now available, and partly from having at hand better information about the nature of solids and of radiation damage.

It appears to be too early to attempt a synthesis of the results into catalytic theory. This is partly because of the lack of sufficient examples, and partly because no detailed characterization of the radiation damage in particular cases has been made. Ultimately, measurements of such properties as electrical conductivity, Hall coefficient, paramagnetic resonance, luminescence, etc., may be expected to help define the actual defects existing in irradiated catalysts. To date, no interesting correlations are apparent with easily measured properties such as luminescence and paramagnetic resonance, and measurements such as conductivity, difficult with powders, have seldom been attempted (*104*). Attention has been confined largely to chemical variables of catalyst and of substrate composition. Under these circumstances, it seems preferable to indicate the general types of behavior that have been observed, and to discuss in detail only a few of the recent researches which pose particular difficulties of interpretation.

The existence of radiation effects on catalysts is quite certain. Changes in activity by several thousandfold have been observed (*93*), variability with catalyst and with reaction have been demonstrated (see below), and at least seven groups of investigators have reported effects.

A change in activation energy upon irradiation, as well as a change in over-all activity, has been reported in two cases, the H_2-D_2 exchange on silica gel (*94*), where the change was from around 9 to 2 kcal/mole, and in the decomposition of formic acid over copper, where it changed from about 25 to about 13 kcal/mole (*95*). It is particularly satisfying to observe changes in activation energy, since this factor characterizes the catalyst more surely than gross activity. In the absence of serious complications, a new activation energy bespeaks a marked change in the electronic state of the catalyst, either as a whole or in specific centers.

Annealing of the observed changes, that is their disappearance with time at a particular temperature, has been observed over a considerable range of temperatures in different cases. With H_2-D_2 exchange on

irradiated gamma-alumina, it has been observed at −78°C over a few hours for very sensitive, water-poisoned samples (*96*). With the hydrogenation of ethylene on ZnO it occurs in the general range of preparation of the catalyst, around 400°C (*97*). Finally, with the decomposition of formic acid on copper, it occurs around 175°C (*95*). Particularly the lower temperature annealing has been taken as evidence for the participation of the usual radiation damage processes in the catalyst changes.

Six reactions have been employed by the various groups of investigators. Only one catalyst has been studied extensively with two reactions, ZnO with ethylene hydrogenation (97) and with H_2-D_2 exchange (*98*). These were affected by gamma irradiation in opposite directions, the activity for H_2-D_2 being enhanced, that for hydrogenation of ethylene decreased. One more reaction, oxidation of SO_2, showed a decreased rate on gamma-irradiated, as compared with unirradiated, V_2O_5 (*99*). Reactions for which enhancements were observed were: H_2-D_2 exchange over Al_2O_3, SiO_2 and other oxides; double-bond isomerization of hexene-1 over SiO_2 (*100*); dehydrogenation of formic acid over copper (*95*); ortho-para hydrogen conversion over alpha and gamma Al_2O_3, Fe_2O_3, reduced MoO_3, and 90% Al_2O_3–10% MoO_3 (*101*). The variability of the radiation effect with the reaction used to assess activity encourages hope of a real usefulness of the phenomenon. As has been the case with conventional catalytic studies, it may be presumed that careful comparisons of different reactions on the same catalyst will be most illuminating.

Examples already noted indicate that a considerable variety of catalysts has been studied. A number of oxides have been studied with the H_2-D_2 exchange, and the results have varied from zero to a factor of several thousand (*94*, *96*). Likewise, the sensitivity to annealing has shown considerable variation from one catalytic material to another (*94*). Also, the enhancement of the ortho-para conversion has varied from zero with MoO_3 or Fe_2O_3 to rather large factors with alumina, alumina-molybdena, and reduced MoO_3 (*101*). Systematic variation of catalyst composition in radiation studies obviously is called for.

In at least one case already studied the radiation behavior of a catalyst has been shown to depend strongly on the presence of a catalyst poison (*96*). If gamma-Al_2O_3 is evacuated overnight around 525°C, most of the water ordinarily adsorbed is removed. The material is then insensitive to radiation. If it has been evacuated at a lower temperature, leaving more adsorbed water, or if water vapor is added to the drier material, the partially poisoned catalyst, though less active, is sensitive to radiation. The greater the water content, the greater the sensitivity to radiation, and the more rapid the decay of the enhancement after irradiation. Poisoning with ethylene or with H_2 (by heating in H_2) produced similar results.

This raises the question whether all of the radiation effects may prove to depend on the presence of a poison, and may represent either removal of the poison or its transformation by radiation into some promoting material. This would presumably be a less fortunate situation for the use of radiation in catalytic studies, than if changes in the solid were generally responsible. At present, examples are known in which poisoning does not seem to be required for the radiation effect (*94*), but the possibility will have to be examined in each case. Nonmetallic catalysts, most prominent in radiation studies to date, are unfortunately more difficult than metals to study under conditions of reasonable surface cleanliness.

A distinction between heavy particle and electromagnetic radiation effects on catalysts has been observed (*96*). In the case of alumina, bombardment with reactor neutrons or with alpha particles from radon leads to an enhancement in H_2-D_2 exchange activity which is far more stable toward annealing than the gamma ray effect. It is attractive to attribute the gamma ray effects to formation of holes or trapped electrons and the heavy-particle effects to vacancies or interstitials, but the possibility of displacement by gamma rays exists, and examples are known in which annealing of such displacements as measured by physical effects occurs at very low temperatures (*102*).

A few comments on particular experiments appear to be in order, either because these experiments have not been mentioned above, or because some special points bear notice.

The experiments on deuteron-bombarded copper as a catalyst for dehydrogenation of formic acid (*95*) are interesting because of the use of a metal catalyst where only displacements can be retained. It is also noteworthy that the activation energy itself was found to be affected. Full details have not been published, and it is difficult to know how to assess the effect of annealing, since the activity measurements were made in the temperature range where annealing occurred.

A most interesting delayed effect of irradiation upon catalytic activity is that on mill-scale (iron oxide) catalysts for Fischer-Tropsch synthesis of hydrocarbons from $CO + H_2$ (*103*, *104*). Such catalysts are activated by treatment in the stream of reactant gas at around 280°C; the synthesis activity sets in over a day or two as the reduction of the catalyst proceeds. Samples preirradiated with some 3×10^7 rads (around 2×10^{21} ev/g) attained a higher synthesis activity than those not irradiated. This difference began to appear after perhaps 40 hours of operation and persisted thereafter for several hundred hours (to the end of the tests).

It appears that something like the photographic latent image is produced, the exposed material being developable by reduction to give a more active catalyst. An effect of irradiation upon reducibility of NiO has been reported (*105*, *106*).

Three more features of the hydrocarbon-synthesis experiments are worth noting. The effect was not found with catalyst particles greater than about 0.2 mm diameter. Since the particles are uniformly bombarded (gamma rays) some competition between surface chemical reactions and bulk defects would seem to be required. Likewise no effect was found with catalysts prepared by precipitation. They differ from the catalysts showing the effect in that the latter are prepared from mill scale containing SiO_2 and Al_2O_3 as impurities and are impregnated with alkali, while the precipitated catalysts are promoted with alkali and with copper. Finally, no significant difference in composition of the

hydrocarbon products was observed between the more active irradiated catalysts and the less active non-irradiated ones.

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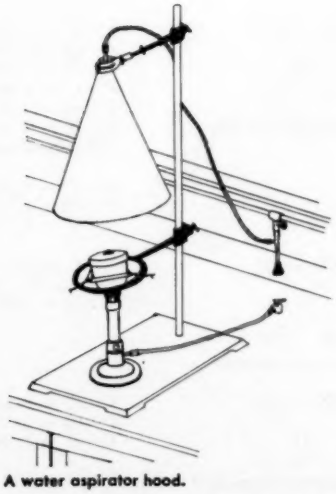
A Water Aspirator Hood

In experiments where noxious gases are given off, the problem of suitable hood space causes many inconveniences and delays. Since many of these gases are water soluble, a hood was devised as shown in the diagram which makes it possible to dissolve the gas in water. The megaphone type funnel was constructed from cardboard measuring 25 centimeters in length with a diameter of 16 centimeters at the large end. The small end of the funnel is adjusted to fit snugly around a number six cork stopper. The cork stopper is fitted with a piece of glass tubing about five centimeters long. Ordinary Scotch tape was used to seal the funnel and hold the stopper in place. The funnel is placed over the source of the gas at a workable height. A Tygon hose connects the funnel to a water aspirator.

The hood was devised for use in the general chemistry laboratory where the problem of hood space is most acute.



A water aspirator hood.

Proceedings of the

Pacific Southwest Association of Chemistry Teachers

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Strain and Interatomic Distances in Small-Ring Molecules

In connection with his research interests of recent years, the author has compiled a table of available molecular structures (configuration, bond lengths, and bond angles) of three- and four-membered organic ring compounds and their derivatives. This compilation is presented here (Table 1) with an accompanying discussion of the effects of strain on molecular dimensions. It is hoped that this table and the discussion, based on relatively simple mechanistic concepts, will prove of interest, since few textbooks give appreciable space to this topic, and much of the published literature is concerned with more complex quantum-mechanical aspects (*1a, b, c*).

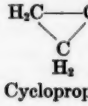
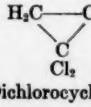
Methods and Reliabilities of the Structure Determinations

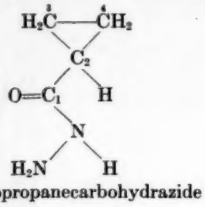
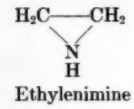
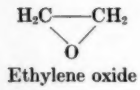
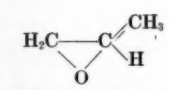
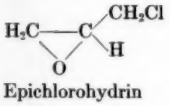
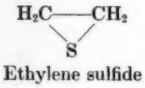
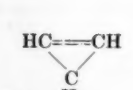
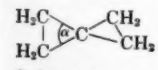
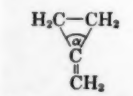
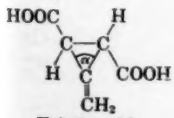
Table 1 contains the bulk of the structures of small-ring molecules which have been determined. Secondary references, not directly related to the structure determination but of structural interest, are also given. Techniques of structure determination have advanced greatly in the last decade, and sometimes caution should be used in considering results of work prior to about 1945. References to readable descriptions of the principal methods are given below.

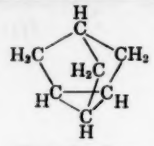
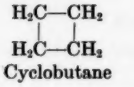
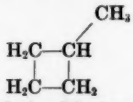
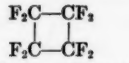
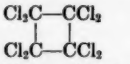
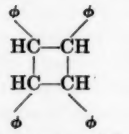
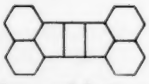
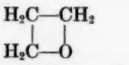
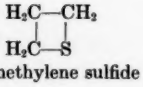
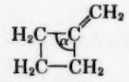
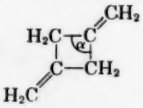
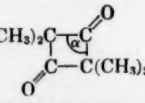
Infrared and Microwave Spectroscopy. The rotational energy of a gaseous molecule is quantized, and from the discrete absorption spectrum of energies in the microwave radio region or infrared light region it is possible to derive very accurately the moments of inertia of the molecule. Relationships between the atomic masses and interatomic separations are derived from these moments, which give, in the very simplest cases, the structural parameters directly; in general, however, for a complete determination, it is necessary to study isotopically substituted molecules also.

Table 1. Structure Data for Small-Ring Compounds

IR = infrared spectroscopy; MW = microwave spectroscopy; ED = electron diffraction; XR = X-ray diffraction; * = based on assumed value; ⊥ = perpendicular to ring plane.

Molecule	Parameters (all distances in Å)	Reference
 Cyclopropane	C—C = 1.526 ± 0.03; C—H = 1.08*; ∠HCH = 109° 28′	(*6*) ED
	C—C = 1.525; C—H = 1.07; ∠HCH = 118.2°	(*7*) ED
	C—C = 1.524 ± 0.014	(*8*) IR
	C—C = 1.524; C—H = 1.07*; ∠HCH ≈ 120°*	(*9*) IR
	C—C = 1.518; C—H = 1.10 ± 0.03; ∠HCH = 116 ± 5°	(*10*) ED
	C—C = 1.511; C—H = 1.086*; ∠HCH = 116°*	(*11*) IR, ED
Cyclopropyl chloride	C—C = 1.52 ± 0.02 C—Cl = 1.76 ± 0.02 C—H = 1.09* ∠Cl—C—⊥ = 34 ± 2°	(*12*) ED
	C—C = 1.47 ∠HCH = 109° C—Cl = 1.755 ∠H—C—Cl = 109° C—H = 1.09 (Unrefined values)	(*13*) MW
	C—C = 1.5131 ∠HCH = 114°36′ C—Cl = 1.7780 ∠H—C—Cl = 120°52.9′ C—H = 1.105	(*83*) MW
Cyclopropyl cyanide	C—C (ring) = 1.5131 ∠HCH = 115°35′ C—C_{CN} = 1.4679 ∠H—C—C_{CN} = 119°35′ C≡N = 1.1574	(*83*) MW
 1,1-Dichlorocyclopropane	C—C = 1.52 ± 0.02 ∠Cl—C—⊥ = 34 ± 2° C—Cl = 1.76 ± 0.02 ∠Cl—C—Cl = 112° C—H = 1.09*	(*12*) ED

Molecule	Parameters (all distances in Å)	Reference
 Cyclopropanecarbohydrazide	$C_3—C_4 = 1.478$ $C_2—C_3 = 1.520$ } 1.506 (av) $C_2—C_4 = 1.493$ } $C_1—C_2 = 1.478$ $C_1=O = 1.213$ $C_1—N = 1.329$ $N_1—N_2 = 1.429$ $\angle C_1C_2\perp = 33°$ $\angle C_3C_2C_4 = 58.8°$ $\angle C_2C_1N = 113.6°$ $\angle C_1NN = 121.3°$	(*14*) XR
 Ethylenimine	C—C = 1.480 C—N = 1.488 C—H = 1.083 N—H = 1.000* $\angle HCH = 116° 41'$ $\angle HN\perp = 22°$ $\angle H_2CC = 159° 25'$ $\angle CNC = 59° 39'$ $\angle CCN = 60° 11'$ $\frac{1}{2}\angle H_2CC - \frac{1}{2}\angle H_2CN = 9° 30'$	(*15*) MW
	C—C = 1.46 ± 0.03 C—O = 1.44* C—H = 1.08* $\angle HCH = 116.7°$ *	(*18*) ED
	C—C = 1.472 C—O = 1.436 C—H = 1.082 $\angle HCH = 116° 41'$ $\angle H_2CC = 159° 25'$ $\angle COC = 61° 24'$ $\angle CCO = 59° 18'$ $\frac{1}{2}\angle H_2CC - \frac{1}{2}\angle H_2CO = 7° 40'$	(*16*) MW
 Ethylene oxide	C—C = 1.470 ± 0.001 C—O = 1.435 ± 0.001 C—H = 1.084 ± 0.002 $\angle HCH = 116° 15' \pm 21'$ $\angle H_2CC = 158° 6' \pm 39'$ $\angle COC = 61° 17'$ $\angle CCO = 59° 11'$ $\frac{1}{2}\angle H_2CC - \frac{1}{2}\angle H_2CO = 7° 42'$	(*17*) MW see also (*10*)
 Propylene oxide	C—C(ring) = 1.471* $C—C_{Me} = 1.513 \pm 0.020$ C—O = 1.436* C—H(ring) = 1.082* C—H(Me) = 1.09* $C—C_{Me} = 1.52 \pm 0.03$ All other parameters assumed from (*16*) $\angle HCH(ring) = 116° 15'$* $\angle HCH(Me) = 109° 28'$* $\angle CCC = 120° 57' \pm 1°$ $\angle C_{Me}C\perp = 33° 47' \pm 1°$ $\angle C_{Me}C\perp = 32 \pm 5°$	(*19*) MW (*20*) ED
 Epichlorohydrin	$C—C_{Me} = 1.52 \pm 0.03$ C—Cl = 1.76* Cl almost *trans* against mid point of C—O bond All other parameters assumed from (*16*) $\angle C_{Me}C\perp = 32 \pm 5°$	(*20*) ED
 Ethylene sulfide	C—C = 1.492 C—S = 1.819 C—H = 1.078 $\angle HCH = 116° 0'$ $\angle H_2CC = 151° 43'$ $\angle CSC = 48° 24'$ $\angle CCS = 65° 48'$ $\frac{1}{2}\angle H_2CC - \frac{1}{2}\angle H_2CS = 4° 37'$	(*16*) MW
 Cyclopropene	C—C = $1.52_5 \pm 0.02$ C=C = $1.28_6 \pm 0.04$ C—H = $1.08_7 \pm 0.04$ (av) $\angle C—C—C = 49° 52'$ C—C = 1.515 C=C = 1.300 C—H = 1.087 ± 0.004 (methylene) 1.070 (vinyl) $\angle C—C—C = 50° 48'$ $\angle HCH = 118°$* $\angle C=C—H = 152° 12'$ $\angle C=C—C = 65° 4'$ $\angle HCH = 114° 42' \pm 10'$ $\angle C=C—H = 149° 55'$ $\angle C=C—C = 64° 36'$	(*21*) ED (*22*) MW
 Spiropentane	C—C(central) = 1.48 ± 0.03 C—C(peripheral) = 1.51 ± 0.04 C—H = 1.08* $\alpha = 61.5 \pm 2°$ $\angle HCH = 120 \pm 8°$	(*23*) ED
 Methylenecyclopropane	C—C(unique) = 1.535 ± 0.015 C—C(side) = 1.484 ± 0.01 C=C = 1.312 ± 0.010 $\alpha = 62° 15' \pm 30'$	(*24*) ED
 Feist's acid	C—C(unique) = 1.545 C—C(side) = 1.494 (av) $C—C_{carboxy} = 1.481$ (av) C=C = 1.317 $\alpha = 62° 45'$	(*25*) XR

Molecule	Parameters (all distances in Å)	Reference
 Nor-tricyclene	C—C(cyclopropane ring) = 1.50 ± 0.02 C—C(other) = 1.54 ± 0.02 ∠CC⊥$_3$ = 19.7 ± 2° See original paper for other parameters	(*26*) ED
 Cyclobutane	C—C = 1.56$_8$ ± 0.02 ∠HCH = 114 ± 8° C—H = 1.09$_6$ ± 0.04 Ring non-planar(D_{2d} or D_{4h} symmetry) with dihedral angle −20°) 20°(+10°,	(*27*) ED see also (*28*, *29*)
 Methylcyclobutane	C—C(ring) = 1.56 ± 0.03 ∠CCC$_{Me}$ ≈ 118° C—C$_{Me}$ = 1.54 ± 0.06 Angle between C—C$_{Me}$ and ⊥ adjacent C—C—C plane = 40 ± 8° Non-planar ring; dihedral angle about 20–30°	(*30*) ED
 Octafluorocyclobutane	C—C = 1.60 ± 0.04 ∠FCF = 109.5 ± 3° C—F = 1.33 ± 0.02 ∠CCC ≈ 89° Non-planar ring; dihedral angle 20 ± 4°	(*30*) ED see also (*31*, *32*)
 Octachlorocyclobutane	C—C = 1.59 (av) ∠CCC = 87.7° (av) C—Cl = 1.74 (av) ∠Cl—C—Cl = 109.4° (av) C...C = 2.20 (av) Non-planar ring; dihedral angle about 22°	(*33*) XR
 1,2,3,4-Tetraphenylcyclobutane	C—C(ring) = {1.555 ± 0.02 / 1.585 ± 0.02} 1.570 (av) C—C(φ) = 1.388 (av) ± 0.021 (max dev) C—C$_φ$ = 1.504 (av) ∠C$_φ$C⊥$_4$ = 45° (av) ∠⊥$_4$⊥$_φ$ = {92° / 39°} C$_4$ ring planar; φ very nearly regular planar hexagons	(*34*) XR
 Dinaphthylene cyclobutane; acenaphthylene dimer	C—C(cyclobutane ring) > 1.54 Not completed	(*35*) XR
 Trimethylene oxide	C—C = 1.54 ∠COC = 94.5° C—O = 1.46 ∠CCC = 88.5° } assumed equal ∠CCO = 88.5° } C—C = 1.55$_3$ ± 0.03 ∠COC = 94.2 ± 2.5° C—O = 1.45$_7$ ± 0.02 ∠CCC = 86.8 ± 2.5° ∠HCH = 113° 38′* (av) ∠CCO = 89.5 ± 2.5° C—C = 1.55 ∠CCC = 84° C—O = 1.44 ∠C...C—H$_2$ = 4° C—H = 1.09 ∠HCH = 110° (adjacent to O) C—H = 1.08 ∠HCH = 111° (opposite O) Planar	(*36*) ED (*37*) ED (*22*) MW see also (*38*)
 Trimethylene sulfide	C—C = 1.54$_9$ ± 0.03 ∠CSC(max) = 78.0 ± 1° C—S = 1.85$_1$ ± 0.02 ∠CCC(max) = 97 ± 5° Large out-of-plane vibrations	(*37*) ED see also (*39*)
 Methylenecyclobutane	C—C = 1.56 ± 0.03 (av); C=C = 1.34 ± 0.02; α = 90° C—C = 1.55 ± 0.02 (av); C=C = 1.34 ± 0.03; α = 92.5 ± 2° Coplanarity assumed, but investigation inconclusive	(*40*) ED (*41*) ED
 1,3-Dimethylenecyclobutane	C—C = 1.526 ± 0.012 α = 92.5 ± 1° C=C = 1.328 ± 0.012 Ring non-planar; dihedral angle = 5 ± 5°	(*24*) ED
 Dimethylketene dimer	C—C(ring) = 1.56 ± 0.05 α = 93 ± 6° C—C$_{Me}$ = 1.54 ± 0.05 ∠C$_{Me}$—C—C$_{Me}$ = 111 ± 6° C=O = 1.22 ± 0.04	(*42*) ED see also (*43*)

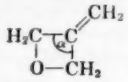
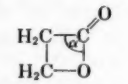
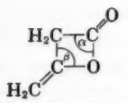
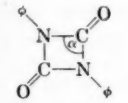
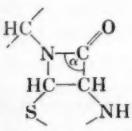
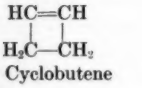
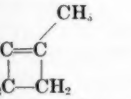
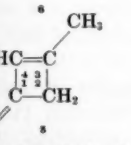
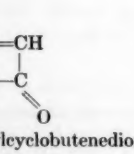
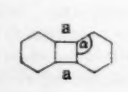
Molecule	Parameters (all distances in Å)	Reference
 3-Methylenetrimethylene oxide	C—C = $1.53_8 \pm 0.02$ C—O = $1.45_8 \pm 0.03$ $\quad \alpha = 86.7 \pm 3°$ C=C = $1.33_3 \pm 0.02$ $\quad \angle COC = 92.8°$ Coplanarity assumed	(*37*) ED
 β-Propiolactone	C—C = 1.53 ± 0.03 (assumed equal) C—O = 1.45 ± 0.03 (ditto) $\quad \angle COC = 89 \pm 3°$ C=O = 1.19 ± 0.03 $\quad \angle C—C=O = 143 \pm 3°$ $\alpha = 94°$	(*43*) ED see also (*44*)
 Ketene dimer; diketene	C—C = 1.52 ± 0.04 $\quad$ C=C = 1.31 ± 0.04 C—O = 1.41 ± 0.04 $\quad$ C=O = 1.19 ± 0.04 $\angle COC = 89 \pm 4°$ C—C = {1.54 in C—C=C; 1.51 in C—C=O} C=C = 1.32 C—O = {1.47 in O—C=C; 1.39 in O—C=O} C=O = 1.22 $\angle COC = 90°$ $\quad \angle C—C=C = 142°$ $\angle CCC = 83°$ $\quad \angle C—C=O = 141°$ $\alpha = 91°$ $\quad \beta = 96°$ Planar	(*43*) ED (*45*) XR
 Phenyl isocyanate dimer	C—C(φ) = 1.37 (av) ± 0.02 (max dev) C—N(ring) = {1.42; 1.49} ± 0.010 C_ϕ—N = 1.41 ± 0.010 $\quad$ C=O = 1.15 ± 0.010 $\angle CNC = 87 \pm 1°$ $\quad \alpha = 93 \pm 1°$ $\quad \angle CNC_\phi$ = {131°; 134°} $\angle O=C—\perp_4 = 87.5°$ $\quad \angle C_\phi N \perp_4 = 79°$ Planar ring	(*46*) XR
 Potassium benzylpenicillin	In the ring: C—C = 1.52 in C—C=O $\quad \angle CNC = 95°$ C—C = 1.51 in C—C—S $\quad \alpha = 90.5°$ C—N = 1.34 in N—C=O $\quad \angle NCC = 86.5°$ } Σ = 359.0° C—N = 1.47 in N—C—S $\quad \angle CCC = 87°$ Attached to ring: C=O = 1.17 $\quad$ N_4—C = 1.47 C—S = 1.84 $\quad$ C_4—N = 1.46	(*47*) XR
 Cyclobutene	C—C = $1.53_7 \pm 0.01_0$ (av) $\quad \angle C=C—C = 94.0 \pm 1.4°$ C=C = $1.32_5 \pm 0.04$ $\quad \Delta(C—C) \leqslant 0.08$ C—H = $1.09_3 \pm 0.01_5$* (av)	(*48*) ED see also (*49, 50*)
 1-Methylcyclobutene	C—C = 1.54 ± 0.03 (av) $\quad \angle C—C—C_{M_e} = 125 \pm 4°$ C=C = 1.34 ± 0.03 $\quad \angle HC=C—CH_2 = 93° 40' \pm 3°$	(*41*) ED
 1-Methylene-3-methylcyclobutene	C_1—C_2 = 1.529 ± 0.015 $\quad \angle C_4C_1C_2 = 88.8 \pm 1.5°$ C_2—C_3 = 1.524 ± 0.015 $\quad \angle C_1C_2C_3 = 84.5 \pm 1.5°$ C_1—C_4 = 1.464 ± 0.020 $\quad \angle C_2C_3C_4 = 93.2 \pm 1.5°$ C_3—C_6 = 1.504 ± 0.015* $\quad \angle C_2C_4C_1 = 93.5 \pm 1.5°$ C_1=C_4 = 1.353 ± 0.015* $\quad \angle C_3C_1C_2 = 134.2 \pm 2.0°$ C_1=C_5 = 1.333 ± 0.015* $\quad \angle C_5C_1C_4 = 137.0 \pm 2.0°$ $\angle H_2C_2H_2 = 116°$* $\quad \angle C_6C_2C_2 = 129.5 \pm 2.5°$ $\angle H_5C_5H_5 = 120°$* $\quad \angle C_6C_2C_4 = 137.3 \pm 2.5°$ $\angle C_2C_4H_4 = 131°$* (Refer to original paper for other simplifying assumptions)	(*24*) ED
 Phenylcyclobutenedione	C=C = 1.340 $\quad \angle C=C—C_\phi = 134.3°$ C—C = 1.505; C=O = 1.196 (in φ—C—C=O) C—C = 1.463; C=O = 1.230 (in H—C—C=O) C—C = 1.536 (in O=C—C=O) $C—C_\phi$ = 1.469 $\quad$ C—C(φ) = 1.390 (av)	(*51*) XR
 Biphenylene	C—C(*a*) = 1.46 ± 0.05 $\quad$ C—H = 1.10* C—C(φ) = 1.41 ± 0.02 $\quad \alpha = 121 \pm 3°$ C—C(*a*) = {1.44; 1.58} ± 0.1 C—C(φ) = {1.37; 1.39} ± 0.1	(*52*) ED (*53*) XR

Table 2. Reference Distances

Bond	Standard distance (in A)	Sources and references
	1.540	Based on values for ethane [1.536 (*55, 56*), 1.543 (*57*)] and diamond [1.544 (*58*)]
	1.502	Based on values for propene [1.498 (*24*)], and *cis*-butene-2 [1.504 (*24*)]. *Cf.* isobutene [1.505 (*24*)] and ethaldehyde [1.501 (*59*)]
	1.338	Based on values for propene [1.338 (*24*)], isobutene [1.336 (*24*)], and *cis*-butene-2 [1.343 (*24*)]. *Cf.* ethylene [1.334 (*60*), 1.337 (*61*), 1.339 (*62*)]
	1.474	Based on values for methylamine [1.474 (*63, 64*), 1.48 (*65*)]. *Cf.* methylamine hydrochloride [1.465 (*66*)]
	1.427	Based on values for methyl alcohol [1.421 (*67*), 1.434 (*68*), 1.427 (*69*), 1.428 (*70*), 1.426 (*71*)]
	1.817	Based on values for methyl mercaptan [1.815 (*72*), 1.8170 (*73*), 1.8177 (*74*)]

(Otherwise, some of the less important distances and angles are assumed, and such assumptions may limit the accuracy of the final result.) Complete and highly accurate determinations of small molecules are now frequently found in the literature. Limits of error of 0.005 Å and less are common in this work (*2a, 3*).

Electron Diffraction. The scattering from a beam of monoenergetic electrons passing through a gas jet in a vacuum chamber is recorded on a photographic plate perpendicular to the beam as a series of diffuse concentric rings. Analysis of this scattering pattern leads to a determination of interatomic distances in the gaseous molecule. For molecules of moderate complexity, limits of error of from 0.01 to 0.03 A on principal interatomic distances have been common in the past; however, improved methods of taking the photographs and refining the structural parameters have given results in recent years comparable in accuracy to those based on microwave measurements (*2b, 4a*).

X-ray Diffraction. Not only the structure of the individual molecules but also how they pack in the crystal is determined by this method, in which a single crystal is placed in a beam of monochromatic X-rays which are diffracted by the regular spacing of the atoms in the crystal; these diffracted X-rays are recorded as spots on photographic film or, for greater accuracy, measured individually by a counter tube (Geiger or other type). From the intensities and positions of these spots the shapes and relative locations of the molecules in the crystal are deduced. Refinement frequently gives standard errors of 0.01 to 0.04 Å; in certain studies in recent years the accuracy has been even better. (Hydrogen atoms, however, are usually difficult to locate accurately by X-ray methods) (*2c, 4b, 5*).

Characteristic Features of Small Rings

All three- and four-membered organic ring molecules are highly strained. Strain energy may be defined for our purposes as the extra potential energy stored (in various ways; see below) in a molecule having at least one bond angle constrained to differ from its normal value. Thus, for example, the 60° and 90° ring angles in cyclopropane and cyclobutane differ significantly from the normal tetrahedral value of 109° 28′ for bond angles at carbon; these molecules have strain energies per mole of 9.2 and 6.5 kcal/CH_2, respectively (*27, 54*). (Cyclopentane has 1.3 kcal/CH_2 strain energy, cyclohexane none.) Chemically, this results in such well-recognized behavior as the great reactivity of cyclopropane (and, to a lesser extent, of cyclobutane) relative to other saturated hydrocarbons; less well known are the structural consequences, resulting partly from use of some of the strain energy to bend, and stretch or compress, bonds in the molecule.

By perusal of the data in Table 1, two generalizations about small-ring structures can be made immediately. One is that bond distances in three-membered rings tend to be shorter than normal (as, for example, in cyclopropane, with C—C = 1.525 Å); another is that distances in four-membered rings tend to be rather long (as in cyclobutane with C—C = 1.568 Å). In addition it appears in many cases that a decreased ring angle at a methylene is associated with a widening of the H—C—H angle (especially noticeable in the three-membered series).

Causes of Anomalous Distances in Small Rings

The anomalous bond lengths mentioned above have been the subject of much discussion, most of it on a more advanced level than employed here. For the sake of visualization on an intuitive physical level, however, it is convenient to describe the causes of these abnormal distances by the concepts of "bent-bond shortening" and "cross-ring repulsion"; in many molecules the effect of a third factor, "differential bond-angle strain," is superimposed on changes from the other two.

It is also convenient with regard to these concepts to think of small-ring molecules in terms of a mechanical analogue, something like the traditional ball-and-stick model. The "bonds" are made of rather stiff springs fixed at normal, unstrained angles in rubber ball "atoms;" two weaker diagonal springs, in the four-membered rings, simulate the cross-ring repulsions discussed below. The potential force corresponding to a change from normal in a bond angle is provided in our model by deformation of the rubber-ball atoms as well as some bending of the spring bonds themselves.[1] The reader may find it helpful to bear this model in mind in the ensuing discussion.

Table 2 is a list of reference interatomic distances. These are taken from reliably determined structures of relatively simple unstrained compounds, and will be used below as comparison standards; Table 3 gives some bond-stretching force constant ratios. A

[1] Such a model would also show the characteristic widening of the H—C—H angle when the skeletal bonds of a ring carbon are forced closer together, as noted in the previous section.

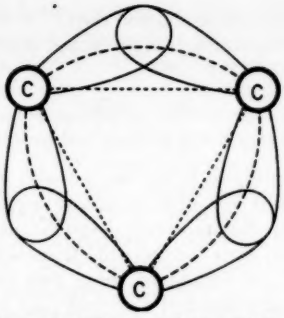


Figure 1. Bent-bond shortening: skeletal orbitals in cyclopropane molecule, showing bonds (long dashes) bent away from internuclear directions (short dashes). Cf. refs. (*1b*, *76*); see also Mashima, M., *J. Chem. Phys.*, 22, 1785 (1954).

stretching force constant is defined for a small change in bond length, Δr_{A-B}, produced by a force t_{A-B}, by the equation: $t_{A-B} = k_{A-B}(\Delta r_{A-B})$. See, for example, ref. (*3*), pp. 14, 26, 195, 331.)

Bent-Bond Shortening. If we consider, with reference to the model described, the deformation of a C—C—C angle from its normal value of 109° 28′ to, say, 60°, a shortening of the C—C internuclear distance would occur because of the bending of the C—C bonds; this "bent-bond" or "banana-bond" concept is useful for explaining qualitatively the short (1.525 Å) C—C bonds in cyclopropane (*76*, *77*). In valence theory language, we would say that the normal tetrahedral orbitals on carbon are not able to bend toward each other as close as 60°, so that the maximum overlap of orbitals on adjacent carbons (and hence the line of maximum electron density defining the true bond) curves away slightly from the straight internuclear line. In three-membered rings, this shortening can be empirically estimated (from cyclopropane) to be 1% of the normal bond length;[2] in four-membered rings the shortening is probably much less significant, perhaps $^1/_8$%.

Cross-Ring Repulsions. A repulsive force between diagonally opposed (non-bonded) carbon atoms has been proposed (*27*) to explain the long C—C bond

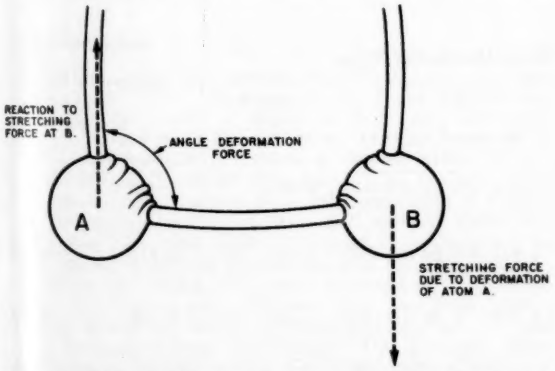


Figure 2. Schematic drawing of portion of rubber-ball-atom and spring-bond model of strained molecule, showing how angle deformation energy stretches neighboring bond; the forces at *A* and *B* are of equal magnitude.

[2] In a more elaborate treatment the shortening should perhaps be made inversely proportional to the bond-stretching force constant; this refinement is ignored here except for the extreme case of the double bond, where the shortening is assumed to be about $^1/_8$%.

length (1.568 Å) in cyclobutane; allowing for a bent-bond shortening of 0.005 Å (see above) the cross-ring repulsive force lengthens each C—C bond in cyclobutane by 0.033 Å, or more than 2%. In other four-membered ring molecules the increase would depend on the magnitude of the repulsive energy and the stretching force constants of the individual bonds. There is also a small strain energy of adjacent CH_2 groups, and in C_4Cl_8 and C_4F_8 the repulsion between halogen atoms on adjacent carbons may also contribute to the even longer C—C bonds of 1.59 Å and 1.60 Å, respectively (*30*).

Differential Bond-Angle Strain. Referring again to the rubber-ball-and-spring model, it will be seen that if the angle deformation energy of one of the rubber-ball atoms (corresponding to a compression of the bond angle from normal) differs from the others in the ring,

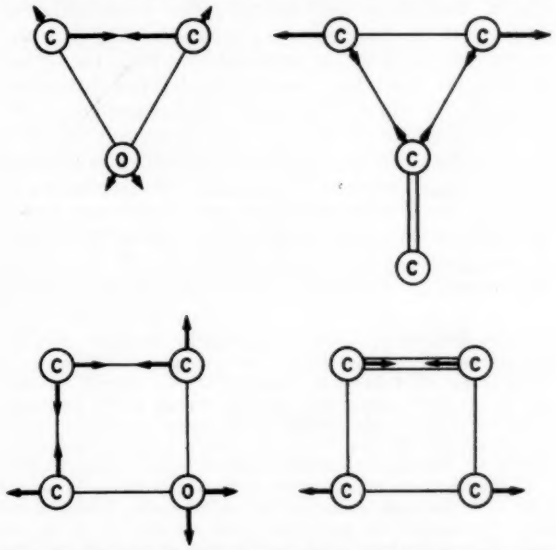
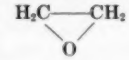


Figure 3. Examples of differential bond-angle strain for various idealized molecules (see text), showing only skeletal atoms and omitting bent-bond effect.

unequal strains will be set up in the ring bonds; this is the general case of a heterocyclic ring, or one in which the skeletal atoms are not exactly equivalent. The angle deformation energy of an atom, transmitted by an attached bond, becomes a strain force on a neighboring bond, giving rise at the same time to an equal but opposite "reaction" force.[3] The resultants of these forces, "differential bond-angle strain," compress and stretch the various bonds.

As the reader can verify for himself, these angle strain forces and their reactions exactly cancel out for the highly symmetrical cases of cyclopropane and cyclobutane.[4] On the other hand, if each carbon in, for example, the less symmetrical ethylene oxide,



[3] This pair of forces is at right angles to the "transmitting" bond; components of these forces are taken along the directions of the other bonds. The effect of the bending of the bonds is neglected in this approximation.

[4] Since the four carbon atoms in either the olefinic or resonating form of cyclobutadiene are also exactly equivalent, no differential bond-angle strain is predicted for this molecule, should it ever be made.

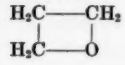
Table 3. Force Constant Ratios

Stretching force constant ratio	Value	Reference
k_{C-C}/k_{C-S}	1.48	Based on stretching force constant values quoted in (*76*)
k_{C-C}/k_{C-O}	0.78	
k_{C-C}/k_{C-N}	0.93	
$k_{C-C}/k_{C=C}$	0.47	

has a greater angle deformation energy than the oxygen atom does (as seems reasonable) the angle strain forces do not cancel out, giving rise to a compressive force in the C—C bond and a stretching force about half as large in each C—O bond.[5] A similar result is obtained for ethylene sulfide, ethylenimine, and cyclopropene, i.e., the unique bond is compressed while the other two bonds are stretched by a force half as large. But in methylene cyclopropane the angle-stiffening property of the double-bond reverses the situation, and the unique ring bond is stretched by a force twice that compressing the other two ring bonds; this latter case is also that found in Feist's acid and spiropentane.[6]

An alternative view of this important effect is obtained by considering what would happen in ethylene oxide, say, if the three ring atoms were suddenly free to move an infinitesimal distance. The more highly strained carbon atoms would tend to relieve their strain at the expense of the less strained oxygen by stretching the opposed C—O bonds; as this occurred the resulting reaction would tend to shorten the C—C bond.

By similar reasoning it is predicted that in trimethylene oxide,



the C—C bonds are being compressed and the C—O bonds stretched by approximately equal forces (exactly equal if the molecule were a perfect square); this situation also occurs in trimethylene sulfide. (Since the C—C bonds in these two four-membered rings are being stretched by cross-ring repulsions and simultaneously compressed by differential bond-angle strain, relatively little net change in the length of these bonds from their standard value (see Table 2) is expected compared to the C—O and C—S bonds, which are being stretched by both these forces. This is in accord with the experimental results listed for these molecules in Table 1.) In methylenecyclobutane the ring bonds adjacent to the double bond are compressed, the other two stretched (just the reverse of the trimethylene oxide case), and in cyclobutene the double bond is compressed and the opposed bond stretched by approximately equal forces, while the two side bonds are under (almost) no net strain from this source.

Some Calculations

At least two major obstacles stand in the way of simple a priori calculations of small-ring structures by methods of plane statics: bond angles have changed so far from normal, especially in the three-membered rings, that the simple harmonic potential function cannot be assumed, and in four-membered rings it is difficult to assess the magnitude of the cross-ring repulsion potential. For three-membered rings, however, some check on the ideas presented here can be made by finding the ratio of the predicted lengthenings and shortenings of bonds, equivalent to solving the following problem: given one experimentally determined bond length of a structure, calculate the other.

Consider, then, as an example of the results given in Table 4, ethylene oxide. The observed C—C bond is

[5] Considered as a problem in plane statics, the more exact and general result is obtained that, for three-membered rings with one atom unique, $t_{C-O}/t_{C-C} = -\cos \angle C-C-O$, where t is the tension in the bond; this result does not depend on the particular bonds involved or the relative angle strain energies. For an equilateral triangle, $\cos 60° = 1/2$, which is the approximation used here. See ref. (*78*) for an analytic treatment of this topic.

[6] Spiropentane is an exception to the simple theory presented here, since the large strain at the central carbon would be expected to lengthen the peripheral bonds and shorten the central ones, whereas it is found (see Table 1) that, although the relative lengths show the expected difference, all the bonds are shorter than in cyclopropane. An explanation has been suggested (*23*), but the molecule is of sufficient interest to warrant, perhaps, a confirmatory structure investigation.

Table 4. Calculations for Three-Membered Rings

Molecule	Given bond (obs.)	Calculated change in other bond	Standard length of other bond (corrected)	Expected length of other bond	Other bond length (obs.)	$r_{obs} - r_{calc}$
	C—C = 1.470	$1/2(1.525 - 1.470) \times 0.78 = +0.021$	$1.427 \times 0.99 = 1.413$	1.434	1.435	0.001
	C—C = 1.492	$1/2(1.525 - 1.492) \times 1.48 = +0.024$	$1.817 \times 0.99 = 1.799$	1.823	1.819	−0.004
	C—C = 1.480	$1/2(1.525 - 1.480) \times 0.93 = +0.021$	$1.474 \times 0.99 = 1.459$	1.480	1.488	0.008
	C—C = 1.515	$-2(1.515 - 1.502 \times 0.99) \times 0.47 = -0.026$	$1.338 \times 0.995 = 1.331$	1.305	1.300	−0.005
	C—C(side) = 1.484	$2(1.502 \times 0.99 - 1.484) = +0.006$	1.525	1.531 (unique C—C)	1.535	0.004

shorter (compressed because of differential bond-angle strain) than in cyclopropane by 1.525—1.470 = 0.055 Å; a stretching of each C—O bond is predicted, as noted before, corresponding to half the C—C compressive force (in the equilateral approximation). Taking 0.78 for the ratio of the bond-stretching force constants, k_{C-C}/k_{C-O},[7] a C—O bond lengthening of $(1/2) \times (0.055) \times (0.78) = 0.021$ A is calculated. This is then added to the standard C—O bond length corrected for a 1% bent-bond shortening: 1.427–0.014 = 1.413 Å. The calculated C—O bond length, 1.413 + 0.021 = 1.434 Å, is in good agreement with the observed value, 1.435 Å; results for other molecules are also in reasonably good agreement with the experimental values.

Conclusion

Using the structure data collected in Table 1 an attempt has been made to show that strain energy of small-ring compounds is not stored solely in distorted bond-angles, but may also bend bonds, and stretch or compress them, with observable effects on bond distances in these molecules. Through the use of concepts based on an artificial model of a ring molecule, some degree of correlation and a simple basis for qualitative discussion have been provided.

Although only organic small-ring molecules have been discussed here, the same concepts would also bear on small-ring inorganic molecules as well (diborane derivatives, for example (*79*)). An example of strain in an inorganic molecule is provided by P_4, with a strain energy per mole of 5.7 kcal/P atom (*80, 82*).

Examples of alternative points of view and further reading on the matters discussed in this paper may be found in (*1a, b, c, d, 54, 81*).

Acknowledgment

This investigation was supported by the Office of Ordnance Research, U. S. Army. The author also thanks Prof. V. Schomaker for many helpful discussions, and Profs. N. Kharasch and J. Donohue for reading the manuscript and offering much constructive criticism.

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Chem Ed

LETTERS

To the Editor:

Over the past few years, two surveys were conducted to obtain information germane to a discussion of the place of qualitative analysis in chemistry curricula. The results of these surveys may be of value to your readers.

Survey I. Questionnaires were mailed to 100 schools, chosen arbitrarily from the 1955 American Chemical Society list of Approved Schools. Fifty-eight completed replies were received, including a good representation of schools with varying enrollment, geographical location, and relative emphasis on science. Of the 58 schools, 25 do not offer qualitative analysis as a separate course; whereas the remainder do. By comparison with previous published reports[1] it is seen that the tendency to integrate qualitative analysis into general chemistry courses continues to increase. This integration may be accomplished without an increase in class and laboratory hours.

[1] See J. Chem. Educ., **17**, 220 (1940); *Ibid.*, **27**, 675 (1950); *Ibid.*, **31**, 365 (1954).

Types of General Chemistry Courses

	No. of schools
(1) May or may not include qual. but not leading to quant. anal.	51
(2) Including qual. leading to quant. anal.	49
(3) No qual. but leading to integrated qual.-quant. courses	2
(4) First semester general, second semester qual.	3
(5) No separate qual. course	25
(6) Separate qual. course	33

Survey II. Questionnaires were mailed to 80 chemical and allied companies. Seventy-six replies were received. Thirteen companeis answered yes to the query—"qualitative inorganic analysis does not possess an important function in our organization." The remaining companies overwhelmingly replied that the classical analytical procedures of separation and identification currently taught in most schools possess little practical value. Instrumental analysis and organic reagents to a lesser extent are mainly used in this field. Several companies emphasized that the value of qualitative analysis lies in the principles, inorganic reactions, and manipulative techniques that may be studied.

Frank Bresci a

City College of New York
New York 31

Report of the New England Association of Chemistry Teachers

Official Business

299th Meeting, February 14, 1959

The 299th meeting was held at the new campus of the Rhode Island College of Education, 600 Mt. Pleasant Street, Providence, and the following speakers were presented: Raymond Thornton, Arnold Hoffman Company, Providence, Rhode Island, "The Impact of Modern Scientific Thought on the Old Crafts of Dyeing and Printing Textiles." V. V. Lindgren, American Cyanamid Company, New York City, "The Training and Utilization of Chemists in the Plastics Industry of the U.S.S.R." Mary M. Keeffe, Department of Biology, Rhode Island College of Education, "The Impact of Biochemistry on General Biology Courses."

300th Meeting, April 11, 1959

Taking advantage of the presence in New England of members of the American Chemical Society who attended the Boston Spring Meeting, the 300th meeting of NEACT was held jointly with the Connecticut Valley Section of the American Chemical Society at Hamden High School, Hamden, Connecticut, and presented as featured speaker, Harry H. Sisler, Head, Department of Chemistry, University of Florida. Dr. Sisler's talk concerned "Recent Developments in the Chemistry of Nitrogen and Phosphorus Compounds." Other speakers were George H. Berthold, Olin Mathieson Chemical Corporation, New Haven, Connecticut, who spoke on "A Contribution of Education to Modern American Industry," and George Adler, Brookhaven National Laboratory, who presented an illustrated talk on "Radiation Induced Solid State Polymerization."

301st Meeting, May 9, 1959

The 301st meeting of the NEACT was held at the Roxbury Latin School, West Roxbury, Massachusetts. Besides the usual features of speakers, luncheon, and business meeting, the Annual Meeting was also held, with the election of officers for 1959–60. The report of the annual meeting appears below.

The program of speakers was as follows: William E. Gordon, Arthur D. Little, Inc., "Combustion in Rockets and High Explosives." Edward Wilson Merrill, Massachusetts Institute of Technology, "Determination of Molecular Weights of High Polymers." Paul D. Grindle, President, Ealing Corporation, discussed the decision of his company to import Russian developed and manufactured laboratory equipment and the reverberations that have resulted.

59th Annual Meeting, May 9, 1959

The meeting was presided over by Robert D. Eddy, Tufts University, the retiring president of NEACT. Some highlights have been gleaned from reports of officers that may be of general interest.

The secretary reported briefly on the events of the year, including the 20th Summer Conference at the University of Rhode Island, and the five divisional meetings. Membership had grown from 732 on May 10, 1958, to 792 on May 9, 1959. Besides active members there are 21 honorary members, of whom 11 are also active, and 6 student members. During the year 114 persons joined the NEACT, more than replacing the 62 who were removed from the membership roster for various reasons.

Avery A. Ashdown, treasurer of the endowment fund, reported that the fund had grown to $2902.87, in spite of the withdrawal of $83.50 interest to help support the publications of the Association. Howard I. Wagner, Edwin O. Smith High School, University of Connecticut, was reappointed as editor of the NEACT *Newsletter*, with Angela Trovato, Branford High School, Branford, Connecticut, as Assistant Editor.

Laurence S. Foster, Watertown Arsenal, Watertown, Massachusetts, submitted his resignation from the editorship of the NEACT *Report*, which appears regularly in THIS JOURNAL. He had been editor of the quarterly that the Association published prior to joining the JOURNAL in 1942. Except for a five-year interruption during the war years, when Leallyn B. Clapp and Lawrence H. Amundsen served their terms as editors, Dr. Foster has been connected with the *Report* since 1938. Lawrence H. Amundsen inaugurated the *Newsletter*, during his editorship, in 1946, and the Editor of the *Report* served as Editor of the *Newsletter* as well until 1955. At the current annual meeting, the Executive Committee of NEACT announced that Robert D. Eddy had been elected as the new editor of the *NEACT Report*, beginning with the January, 1960, issue. It was voted that the secretary send to Laurence S. Foster the sincere thanks of the Association for his services as Editor of the *Report*.

The Chairman of the Honorary Membership Committee, Marco H. Scheer, read the following citations of members who were elected to Honorary Membership:

AVERY A. ASHDOWN: for 25 years a member of the New England Association of Chemistry Teachers; Treasurer of the Endowment Fund and oft-time participant in the affairs of our organization; long-time member and guiding force of the Northeastern Section of the American Chemical Society, and editor of its publication, the *Nucleus;* author of many publications; for many years a faithful teacher at the Massachusetts Institute of Technology. The New England Association of Chemistry Teachers is honored to confer upon him the status of Honorary Membership.

CARROLL B. GUSTAFSON: for 18 years a member of the Association and for thirteen years, its treasurer; long active in the preparation of our *Newsletter;* active participant and often committee member in our affairs; author of a textbook and other publications in his chosen field; a faithful teacher at the Massachusetts College of Pharmacy; member of the American Chemical Society and the American Pharmaceutical Association. The New England Association of Chemistry Teachers is honored to confer upon him the status of Honorary Membership.

GEORGE DAVID HEARN: for 24 years a member of the Association, and for 47 a member of the science teaching profession, 30 years of which were spent in teaching chemistry and 20 as head of the department of chemistry, is well remembered for his many contributions to Summer Conferences. He served on the General Committee of the Sixth Summer Conference, and was Chairman of the Eleventh. The following year he took complete charge of all hospitality. At several others he was in charge of the movies and at a Conference in Maine, he arranged not only the usual book exhibit, but an industrial exhibit as well. He also served on a nominating committee. Throughout his years of membership he faithfully and regularly attended divisional meetings, and saw to it personally that fellow-members, not so well provided, were assured of transportation. Welcome always for his unfailing good humor, his unflagging optimism and his ready hand of assistance, this citation comes as an added star to the crown of his retirement.

Evelyn L. Murdock, of Westerly, Rhode Island, was elected to the Nominating Committee for the three years, 1960–62. The other members of the committee are Louise O. C. Swenson, *Chairman* (1960), and Francis Lamoureaux (1961). Phyllis Brauner of Simmons College was designated as Publicity Agent for a second term.

The makeup of the Board of Trustees of the Endowment Fund is as follows: Avery A. Ashdown, through June, 1960; Elbert C. Weaver, through 1961; and Mary B. Ford, through 1962.

Upon receipt of the report of the nominating committee, the following slate of officers was elected for the year 1959–60:

President: Carl P. Swinnerton, Pomfret School, Pomfret, Conn.
Vice-president: Leallyn B. Clapp, Brown University, Providence, R. I.
Secretary: Rev. Joseph A. Martus, S.J., College of the Holy Cross, Worcester, Mass.
Treasurer: Carroll B. Gustafson, Massachusetts College of Pharmacy, Boston, Mass.
Divison Chairmen
Northern Division: Maurice M. Whitten, Gorham State Teachers' College, Gorham, Me.
Central Division: Richard M. Whitney, Roxbury Latin School, West Roxbury, Mass.
Southern Division: Russell Meinhold, Rhode Island College of Education, Providence, R. I.
Western Division: Norman W. Lafayette, Hamden High School, Hamden, Conn.

Maryalice Moore, Stonehill College, North Easton, Massachusetts, was appointed as *Assistant to the Secretary*, to keep the records and minutes of the Association and of the Executive Committee.

Following the election of officers, the new president, took the gavel of office.

Grube Studio.
Putnam, Conn.

Carl P. Swinnerton

CARL P. SWINNERTON was born in Danvers, Massachusetts, in 1898. He became interested in chemistry while studying at New Hampton Literary Institution, New Hampton, New Hampshire, from which he was graduated in 1916, and concentrated in chemistry at Harvard College where his faculty advisor was Prof. T. W. Richards. After graduation from Harvard in 1921, he returned to New Hampton as teacher of science and mathematics the following year. He received his Master of Education degree at the Harvard Graduate School of Education in 1923. Since then, while on sabbatical leave, he has studied physics at Cambridge University. Prior to 1944, when he was appointed to the faculty of Pomfret School, he taught at the Naugatuck High School, Teachers College in Keene, New Hampshire, Culver Military Academy, Phillips Exeter Academy, and the Shipley School. During World War II he joined the Airborne Instruments Laboratory at Columbia University and after some months became a department head. In 1943 and from 1945 to 1954, he was a member of the Science Committee of the Secondary Education Board and was its chairman for the last four years. Currently he is head of the science department at Pomfret School and is involved in the PSSC program, setting up the physics course at Pomfret and teaching in the NSF summer institute at the University of Connecticut.

He has been active in the affairs of the NEACT since 1939 when he participated in the first summer conference. Subsequently he has been on nine conference committees or programs, served as co-chairman (with John A. Timm) in 1948 and as secretary in 1949 and 1950. He was chairman of the Western Division in 1949 and was elected Vice-President of NEACT in 1957.

In 1935 he married Natalie Marshall, a classmate at New Hampton. She and their son John have become well known in summer conference activities. Through his hobby of color stereophotography, he has entertained many a summer group with astonishingly beautiful pictures of his extensive travels.

JOSEPH A. MARTUS, S.J., *Secretary*

Help Wanted!

Is there a Science Council in your area?

The Committee on Institutes and Conferences of the Division of Chemical Education, ACS, is compiling information on the names, locations, and scopes of Science Councils in the U.S. Names and addresses of executive offices are essential. Readers are urged to send information to: Dr. Donald S. Allen, Chairman, Department of Chemistry, State College for Teachers, Albany, N.Y.

Chem Ed

BOOK REVIEWS

The Essentials of Chemistry

R. P. Graham and *L. H. Cragg*, Professors of Chemistry, Hamilton College, McMaster University, Canada. Reinhart & Co., Inc., New York, 1959. xi + 579 pp. Figs. and tables. 16.5 × 24 cm. $6.50.

In considering a book which is being introduced into a field as well populated as that of textbooks for beginning chemistry courses, one must, of course, take into account the type of group for which it may have been written. In this case the purpose of the book is stated simply, and broadly, by the authors to be:

(1) This is a textbook carefully planned and written for those who wish to learn (or teach) the essentials of chemistry.

(2) This is meant to be a *textbook*—not a laboratory manual, not a handbook of facts and figures, not a wonder book of chemistry whose main purpose is to make students exclaim, "Isn't science marvellous!"

The physical features of the book binding, type, printing, etc. are good. The illustrations are in general, also, of good quality. The choice of photographs is occasionally rather weak in so far as illustrating any feature of chemistry is concerned; but there are numerous diagrams and drawings which are well drawn.

A real effort has been made to provide aids for study, in the form of questions, exercises, and problems at the ends of chapters, in the appendixes, and in cross-referencing of topics in the text. The "exercises" are questions designed "to stimulate clear thinking" and are in general fairly well chosen, although on occasion they lapse into mere repetition of definitions, etc.

The style is somewhat spotty, partly because there is some predilection for footnotes and parenthetical or side remarks. These often interrupt the reader's chain of thought in an exposition and are on occasion quite poorly chosen—for example, when the very important concepts of atoms and molecules are introduced via a footnote. There are occasional errors or weaknesses in wording for which the teacher must watch, such as the definition of combustion as the chemical union of some substance with oxygen, or the statement that a housewife is "surrounded by colloidal *chemistry*," but these are not serious or really numerous.

The book does have very excellent presentations of such fundamentals as chemical nomenclature and equations, chemical calculations, and the periodic table. The exposition of the use of various units and quantitative relations in problems is one of the best features. The choice and presentation of materials on the chemical properties of the various elements and compounds are also quite good.

In some instances the authors have rather rigidly limited the scope of the book, some in areas of major importance in chemistry. There is, for example, no reference to any deviations from the Gas Laws and the liquid state is covered simply by the statement that the kinetic theory "can *easily* be extended" to include this. There is also an unqualified statement that "electrons move rapidly around the nucleus of the atom in orbits, much as planets move about the sun." The arrangement of electrons is discussed in terms of *K*, *L*, *M* shells, etc. and it is noted that the *M* shell can hold "only" 18 electrons. This is followed shortly without comment by a table showing the 2, 8, 8 arrangement for argon. One instance was noted, with regard to the periodic table and multiple valence, in which the authors stated that the explanation was rather too complicated for this book. The usual approach is simply to ignore such questions.

This approach undoubtedly has its origin in the problem of keeping the amount of material within reasonable limits and it has certain advantages in keeping materials fairly neatly packaged for classroom work. However, very little additional space would be required to bring out some of the limitations in present knowledge and ideas. Moreover, the tendency to avoid mentioning such complications results in a book which in its whole fails to bring out one of the major essentials of chemistry: that it is an active and growing field of study and investigation. Such a book covers the nomenclature and facts but not the science of chemistry.

The authors' explanation, in the Preface, is that they have kept the book relatively short and "have left out nothing that is essential *at this stage* of one's study of chemistry." On this basis the book is suitable only for those students who will have opportunity in later years to learn something of research and the questions ahead in chemistry as well as an outline of present knowledge of elements and compounds.

The book is difficult to evaluate, for it has some very strong features and some quite weak ones. It cannot be given unqualified recommendation for "those who wish to learn (or teach) chemistry." It is not a laboratory manual, a handbook, or a "wonder book" of chemistry; but it still has limitations as a textbook. It is not to be recommended for students for whom this would be the only experience with the study of chemistry. It could be used effectively in the beginning course for groups who will be taking further work in chemistry.

ROBBIN C. ANDERSON
The University of Texas
Austin

General Chemistry Workbook

Conway Pierce, University of California, Riverside, and *R. Nelson Smith*, Pomona College. 2nd ed. W. H. Freeman & Co., San Francisco, 1958. vi + 243 pp. 15.5 × 23.5 cm. Paper bound. $1.75.

This is the second edition of a problem-exercise book for general chemistry which first appeared in 1955. The work covers all of the important types of problems considered in the first year college course.

Each chapter contains a discussion of the principles involved in various calculations followed by one or more solved

Reviewed in this Issue

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George K. Estok, Organic Chemistry. A Short Text

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M. Brezina and *P. Zuman*, Polarography in Medicine, Biochemistry, and Pharmacy

E. Emmet Reid, Organic Chemistry of Bivalent Sulfur. Volume 1

Charles E. Seiverd, Chemistry for Medical Technologists

Morris B. Jacobs, The Chemical Analysis of Foods and Food Products

Carl S. Vestling, Editor-in-Chief, Biochemical Preparations. Volume 6

R. H. Doremus, *B. W. Roberts*, and *David Turnbull*, Editors, Growth and Perfection of Crystals

problems. Then there follow two essentially identical groups of problems or exercises. Answers for one set are in the back of the book.

Explanations are given in a clear orderly fashion. Errors frequently made by beginning students are pointed out. Reason in solving problems is stressed rather than the use of mathematical formulas. There is considerable emphasis on the correct use of dimensional units and significant numbers in chemical computations.

Whereas the original edition explained weight relations in chemical change by both proportion and molar methods, the new edition has deleted the former. Oxidation-reduction equations are discussed from the viewpoint of oxidation numbers and half-reactions. The emphasis is on the writing of ionic equations.

The second edition contains some new problems, but many are in the original work. All problems seem to be well thought out and clearly stated. Practical applications and new chemical processes make many problems of far greater interest than those generally found in the average textbook.

This book should be very useful as a supplementary workbook for the first year course in college chemistry.

E. F. Furtsch
Virginia Polytechnic Institute
Blacksburg

An Introduction to Electronic Theories of Organic Chemistry

G. I. Brown, Assistant Master, Eton College, England. Longmans, Green & Co., Inc., New York, 1958. v +209 pp. 13.5 × 19 cm. $3.

Brown wrote this little book for "advanced sixth-form" and "first-year university" students as a means of expanding their knowledge of the theories of organic chemistry after they know a reasonable body of facts. This appears insufficient reason for its distribution in this country since here beginning textbooks of organic chemistry in recent years are given over to theories of organic reactions and have simply grown larger by virtue of the dual presentation of facts with theories. Fewer and fewer teachers of organic chemistry are forcing students to learn reactions first and theories later.

The topics discussed in some detail on a non-mathematical basis are molecular orbitals, resonance and inductive effects (in the language of the English school), conjugation, hyperconjugation, structure of and substitution in benzene, hydrogen bridging, and reaction mechanisms (the last 48 pages). The discussion of individual topics in the chapter on mechanisms is all too brief for understanding except to the person already familiar with the ideas since the treatment is condensed to say the least.

The discussion on any one subject is too skimpy to satisfy a graduate student in organic chemistry, but it may serve as a refresher for students in other fields of chemistry. It may well serve as a reference for retreading high school teachers in a Summer Institute course where the instructor wishes to give a modern view of theoretical organic chemistry in a week or two without forcing anyone to learn a single reaction. Students who feel lost in reading Ingold or Hine might first want to delve into this book.

In a sense it is a companion to Brown's "A Simple Guide to Modern Valency Theory."

Leallyn B. Clapp
Brown University
Providence, Rhode Island

Science

A course of selected reading. Revised edition. International University Society, Edinburgh, 1957. xxiii + 322 pp. 15.5 × 23.5 cm. $4.50. Sole distributors: Collings, Inc., 507 Fifth Ave., New York.

The usual book on the philosophy of science is frequently more "of" than "science." In contrast, this collection of readings (entirely in English) allows the reader to build his own philosophy by listening to the words of 43 great men of science. It has been selected imaginatively, edited carefully, and presented attractively. All who stop to ask the reflective and far-reaching questions about the role of science in our culture will find this volume rewarding. Those who want to use the apt quotation to help establish a historical perspective may find just the item here. Dalton, Lavoisier, Faraday, Thompson, Aston, Rutherford, and other giants are included.

W. F. K.

Organic Chemistry. A Short Text

George K. Estok, Texas Technological College, Lubbock. W. B. Saunders Co., Philadelphia, 1959. ix + 275 pp. 73 figs. 31 tables. 16.5 × 24.5 cm. $5.50.

This text is designed for one quarter or one semester of organic chemistry and will be a welcome addition to this field, where a concise treatment of organic chemistry is necessary. It is confined to 14 chapters totalling 275 pages, including the index.

On the inside covers are schematic diagrams relating, respectively, to various classes of aliphatic compounds and of aromatic compounds. At the beginning of many chapters are a few well-chosen, enlarged, boldly-printed, typical class compounds. A very few mechanisms of reactions are given, which will be satisfying to most teachers of these short organic courses. Although highly restricted, the student must appreciate the meaning of a reaction mechanism. The tables are clear and concise. Study questions and exercises are excellent and neither too burdensome nor trivial. Aliphatic and aromatic compounds are developed together, which has many advantages over a separate treatment. The photographs are well done, especially those of personalities of historic interest. There are perhaps a few too many pictures of industrial plants, which do not have much teaching value. Two of these, at most, would suffice to inform the student that industrial operations are feats of engineering genius. At the close of many chapters are summaries of important reaction types in precise, tabular form. Many of the more important newer developments in organic chemistry are given. Some errors are found, as is true of all texts. One might wish to see the terms *arenesulfonate* used in place of *aryl sulfonate* and *alkanesulfonate* instead of *alkyl sulfonate*, for example, and the word *glyceryl* should be employed for the *acyl* radical of glyceric acid, rather than for the radical derived from glycerol.

Electronic structure, hydrogen bonding, resonance, and molecular models are included in a sensible way. The author tends toward a scientific approach rather than a popular one, which is in keeping with the present trend in this direction across the nation. Practical applications are emphasized with significant descriptive materials to make them understandable. This text will be very useful in the short course of organic chemistry and will provide the essentials very adequately and attractively.

John Leo Abernethy
Fresno State College
Fresno, California

Organic Syntheses with Isotopes. Part 2

Arthur Murray III and *D. Lloyd Williams*, University of California, Los Angeles Scientific Laboratory. Interscience Publishers, Inc., New York, 1958. ix + 947 pp. Figs. and tables. 16 × 23.5 cm. $25.

Part 2 of "Organic Syntheses with Isotopes" contains chapters 15 through 20, which are devoted to syntheses of compounds of the isotopic halogens, isotopic hydrogen, nitrogen-15, oxygen-18, phosphorous-32 and sulfur-35. Each chapter is further subdivided into classes of compounds appropriate to the isotopic element. Chemical equations summarizing the synthesis precede each description of procedure. The index for both volumes is included at the end of Part 2.

The present volume is in the same form, style, and clarity as Part 1. As with the first volume, there is little to criticize and much to praise. Murray and Williams appear to have given us a truly exhaustive survey of the field of isotopic syntheses; in fact, so exhaustive, and so complete, that it is difficult to see how it could have been accomplished in the present decade. In addition to such data as the results of infrared and mass-spectrographic analyses, which relate to the purity or to the isotopic content of the compounds prepared, the notes following each procedure often contain information of mechanistic importance, or information relating to degradative techniques by which positions of the labels were determined. Further, the book contains tables summarizing vast amounts of data. Table XV (1), for example, is eleven pages in length and

deals with bromine exchange with alkyl bromides. Table XVI (12–29) is sixty-five pages in length and summarizes the reactions and references on deuterium exchange with acids, alcohols, aldehydes and ketones, aliphatic halides, alkanes, alkynes, alkenes, amides, amino acids, aromatic hydrocarbons, carbohydrates, esters, ethers, heterocyclic compounds, nitro compounds, onium compounds, phenols, and miscellaneous compounds. A similar table, XVIII, exists for exchange reactions of oxygen-18. Thus the book is useful in much more than a synthetic sense, and is a source of a really tremendous amount of information for any scientist actively engaged in research with isotopes.

The index is of compounds only, and indicates where in Parts 1 and 2 each is to be found. Although "references to preparations without procedural details are given in italics," the reviewer had difficulty in distinguishing the italicized type from ordinary type. Murray and Williams in this volume, as well as in Part 1, have made such a fine contribution to isotopic chemistry, however, that for the foregoing peccadillos, and for the lack of an author index, they can be easily forgiven.

CLAIR J. COLLINS
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Polarography in Medicine, Biochemistry, and Pharmacy

M. Brezina and *P. Zuman*, Polarographic Institute of the Czechoslovakian Academy of Science, Prague. Revised English ed. Interscience Publishers, Inc., New York, 1958. xviii + 862 pp. 318 figs. 24 tables. 16.5 × 23.5 cm. $19.50

This book first appeared in 1952 in the Czech language. It was revised and expanded to cover the literature through 1954 when it was published in a German edition in 1956. The present translation into English contains most of the material found in the German edition but does not include the introductory chapter on the principles of polarography and the author index as well as some of the formulas and polarograms. The English version is nevertheless 62 pages longer because in it textual headings are used and the references are placed at the end of the chapters. In the German edition space is saved by marginal headings and references in small print as footnotes on each page.

The major sections of the book, Determination of Inorganic Compounds (172 pp.), Determination of Organic Compounds (400 pp.), Proteins (100 pp.), Enzymes (18 pp.), and Polarographic Maxima (22 pp.) are followed by Tables of Important Buffers and Half-Wave Potentials (60 pp.) and a Bibliography of books and review articles on polarography. An index of Materials and Subject Index complete the book.

The present version of the book is intended to be used in conjunction with other texts on polarography since it contains neither general instruction about the method and apparatus nor any theoretical discussions. While a number of particularly well studied analyses are described in detail, most of the analytical applications are only outlined or indicated by a reference. In the case of popular analytical procedures, e.g., the analysis of oxygen, a great many different electrodes and methods are described without any critical evaluation so that the clinician, physiologist, or pharmacologist would have to know polarography well in order to make a suitable choice of method.

The book, therefore, is of most value to the specialist in polarography who will find it a complete and extensively annotated bibliography of polarographic papers through 1954 in the fields indicated in the title. Because many of these have appeared in the Czech language, an English version is particularly welcome. Dr. Wawzonek's translation is excellent. Also the print, paper, and binding of the book are of the usual high standard of the publishers. It is surprising, therefore, that they did not make the contents of the book more readily usable. In order to find a given reference—indicated in the text only by number, not by name—one has to leaf page by page to the end of the particular chapter. Proper page headings would be of help in such a search, but in this book they are "Polarography" on the left side and one of the sectional titles on the right side.

OTTO H. MÜLLER
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Organic Chemistry of Bivalent Sulfur. Volume 1

E. Emmet Reid, Emeritus Professor of Chemistry, Johns Hopkins University. Chemical Publishing Co., Inc., New York, 1958. 539 pp. 15 × 22 cm. $20

The study of organic sulfur compounds has become an increasingly active field of research in recent years. Part of this activity is due to the importance of sulfur compounds in biochemistry, chemotherapy and polymerization processes, and part is due to interest in fundamental problems of reaction mechanism and structure, which abound in the field.

The appearance of the present volume (the first of a series of five) by the distinguished pioneer in the field, Professor E. Emmet Reid, is therefore an event of importance to chemists in many areas.

The series is limited to the chemistry of bivalent sulfur compounds, and the first volume covers the mercaptans, substituted mercaptans and mercaptan acids. The section on mercaptans contains an extensive discussion of the removal of mercaptans from petroleum. The reactions of mercaptans which lead to sulfides and other classes of compounds to be covered in later volumes are not discussed.

The chapter on negative derivatives of mercaptans, however, deals with sulfenic acid derivatives, and various inorganic ester derivatives of mercaptans, including thiophosphoric esters.

The coverage of these classes is encyclopedic, and the series of volumes will be a veritable Beilstein of sulfur chemistry, with all of the advantages and some of the disadvantages which that implies. There is little critical discussion of theoretical questions or of reaction mechanisms, although there are extensive correlations of physical properties, especially of the mercaptans. There is a very complete coverage of the chemical literature, including patents, with extensive lists of compounds and their physical properties, and with leading references to the biological activity of compounds, where it has been examined.

The book has over 4000 references (the whole series has 20,000) and will undoubtedly be the starting point for any literature survey on bivalent sulfur compounds. It will be of great value to research workers in the field, both in industrial and university laboratories.

It would be improper to end with emphasizing the magnitude of the task which Professor Reid has undertaken and finished. There can have been few contributions to the chemical literature of this scope and monumental character, carried through virtually singlehanded, and completed, by a scholar of Reid's years. The reviewer hopes that he will feel repaid for his unselfish labors by the knowledge that his volumes will be of great and continuing value in the future exploration of the field of sulfur chemistry.

D. S. TARBELL
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Chemistry for Medical Technologists

Charles E. Seiverd, Director of Research, The Horizon Laboratories, Glendale, Arizona. The C. V. Mosby Co., St. Louis, Mo., 1958. 465 pp. 17.5 × 25.5 cm. $10.75.

Approximately 80 per cent of this book consists of detailed methods of analysis that were developed and reported in large part prior to 1940, with the selections being governed by the results of surveys the author has used to determine the most popular methods of urine and blood analysis. Thus most of the important developments in determinations and methods since approximately 1940 are either absent or presented too briefly to be of substantial value. The book includes pregnancy tests, function tests for liver and kidney, and conventional methods for the analysis of spinal fluid, and gastric and duodenal contents. A very limited amount of space is devoted to the analysis of feces and milk.

Approximately 100 pages of the sections on analytical methods (326 pages) are taken directly from the laboratory manuals of four different companies that market photoelectric colorimeters and other items used in medical technology. Over one half of this material is from one of the four companies.

In general the methods are clear and in detail. There are numerous drawings and other illustrative material that contribute to the clarity of the presentation. Also, ample directions are given for the preparation of reagents and calibration proce-

dures. The entire book seems to be remarkably free from errors and it is well organized.

Approximately 20 per cent of the book consists of a section on Essentials of Elementary Chemistry which "serves as a fulcrum for the less-advanced student and a review for the more-advanced student." A large proportion of this is devoted to basic techniques, the preparation of solutions, and the operation of colorimeters. The material is accurate, but many of the basic facts and principles of chemistry are either entirely omitted or simplified to such a large degree that students dependent upon this book for a working knowledge of chemistry can hardly be expected to become reliable medical technologists, unless they are under the close supervision of persons well trained in chemistry.

A large number of National Registry type questions and answers are included. There is also a small bibliography, but several of the references are out of date because more recent editions have been published. The book should be useful to students and practicing medical technologists who need to use only the more conventional and simple chemical methods of analysis, but it will not be very helpful in preparing them to understand and use more complicated methods and ideas.

HARRY G. DAY
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Bloomington

The Chemical Analysis of Foods and Food Products

Morris B. Jacobs, Consulting Chemist and Microbiologist. 3rd ed. D. Van Nostrand Co., Inc., Princeton, N. J., 1958. xxiv + 970 pp. 88 figs. 106 tables. 16.5 × 23.5 cm. $13.75.

For 20 years through two editions and several reprintings this book has served as a standard text for the food chemist and analytical chemists in general. The first edition (J. CHEM. EDUC., **16,** 100 (1939)) contained 537 pages; the third edition, 970 pages. Thus, one can see the increase in scope, data, techniques, and procedures which has occurred over 20 years.

The book contains 24 chapters, an appendix with certain tables, and a subject index. In the body of the text are 106 tables and many figures. Representative chapters and areas of analysis include: Coloring Matters in Foods; Milk and Cream; Oils and Fats; and Jams, Jellies, and Fruits. The many analytical procedures usually are adequate, but the treatment of data and interpretation of results are not always clear.

It is unfortunate that the introduction of new material was not accompanied by the deletion of much of the earlier material. The reviewer believes that many pages of this book could well have been omitted. There has been only a little rewriting of the material which appeared 20 years ago, and in this respect one might say that the value of the new edition lies in the introduction of new topics such as radiochemical determinations, artificial sweetening agents, and pesticide residues. The author could well have brought many of the figures up-to-date. Chapter 18, Inorganic Determinations, is quite out of date, for many of the methods are 20–30 years old. Chapter 2, Physical Chemical Methods, could have been brought more up to date. Although new tables have been introduced, none of the earlier objections have been corrected.

This is not an educational text but is a compilation of difficult to find methods of food analysis. As a compilation this book is of value to those interested in such analyses; particularly if one realizes that it should be used in conjunction with the "Methods of Analysis of the A. O. A. C." and such journals as *The Analyst* and *Analytical Chemistry*.

JAMES M. PAPPENHAGEN
Kenyon College
Gambier, Ohio

Biochemical Preparations. Volume 6

Carl S. Vestling, Editor-in-Chief. John Wiley & Sons, Inc., New York, 1958. ix + 105 pp. 15.5 x 23.5 cm. $5.25.

Volume 6 of "Biochemical Preparations" is the best of the recent volumes of this useful series in providing carefully checked procedures which lead to reasonable amounts of needed, difficultly obtainable research materials. This volume also has educational value in illustrating many of the modern preparative techniques of biochemistry.

Many of the shortcomings of the two previous volumes noted by this reviewer (J. CHEM. EDUC., **33,** 1358 (1956); J. CHEM. EDUC., **35,** A616 (1958)) have been eliminated from Volume 6. Preparations essentially biochemical in character have been emphasized. Chromatographic and adsorption methods are used for the isolation of crystalline animal cytochrome C, L-α-glycerophosphorylcholine and old yellow enzyme. The purification of insulin by fibril formation is unusual. An enzymatic method is employed for the preparation of ribulose diphosphate. Especially timely are the description of the isolation of ribonucleic acid and deoxyribonucleic acid. Standard biochemical methods are employed for the isolation of 2,3-diphosphoglyceric acid, lanosterol, leucine aminopeptidase, crystalline horse oxyhemoglobin, crystalline papain, and crystalline muscle phosphorylase *a* and *b*. Typical procedures in organic chemistry are described for the synthesis of 3-hydroxyanthranilic acid, β-hydroxy-β-methylglutaric acid, α-methylserine and bis(hydroxymethyl)glycine, benzoyl-L-argininamide, phosphoserine, and DL-tryptophan-7a-C^{14}. While the versatility of the selected compounds is impressive, it is hoped that in future volumes more peptides, e.g., those related to oxytocin and vasopressin, will be included, since peptides are in tremendous demand in many areas of biochemical research.

The extensive contribution of the editor, Dr. Carl S. Vestling, and his associates at the University of Illinois deserves mention. Of the nineteen preparations, the Illinois group was responsible for checking twelve procedures, with Dr. Vestling personally involved in three checks. One preparation was submitted by this same department. Perhaps future editors of this series might profit by seeking an even greater international flavor to their volumes. No checks were reported from non-U.S.A. labs, although five preparations were submitted from foreign laboratories.

Previously expressed concern about the overlap between this series and the "Methods in Enzymology" series has been largely dispelled. The continual revision of the "Methods" series would obviously be too costly. Thus "Biochemical Preparations" makes its most useful contribution to the biochemist by introducing especially timely procedures which have not been repeated elsewhere.

EARL FRIEDEN
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Tallahassee

Growth and Perfection of Crystals

Edited by *R. H. Doremus, B. W. Roberts,* and *David Turnbull*. John Wiley & Sons, Inc., New York, 1958. xviii + 609 pp. Many figs. 23 × 28.5 cm. $12.50.

This is the best edited set of papers it has been my pleasure to see: the report of a meeting held at Cooperstown, New York, August 27–29, 1958, the printed volumes were distributed in December, 1958. In spite of this short interval, there are very few errors, the illustrations are exceptionally well done, and the format and binding most satisfactory.

The real worth of the collection lies in the individual papers, of course. An introductory paper is followed by sections on: Growth of Whiskers (6 papers), Properties of Whiskers and Crystal Imperfections (11), Growth of Crystals of the Solvent Phase (9), Growth of Crystals of the Solute Phase (7), and Crystallization of Polymers (8). Each section begins with an introductory paper of its own. The papers are of a high quality, almost without exception, recount exceptionally current work, and are presented lucidly and fully by some of the best workers in the field. The illustrations are superb, and are probably the best collection of photographs available in this field. The volume justifies its purchase in terms of them alone.

Most of the papers have an introductory statement, abstract, or summary, are divided editorially by appropriate subheadings, are followed by comments, both oral and written, and conclude with good bibliographies. Both an author and subject index are included for the whole volume.

If the sponsors of future symposia can attain the excellence of this report we may have a new and very valuable type of addition to the scientific literature.

J. A. CAMPBELL
Harvey Mudd College
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